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IN
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MODERN TRENDS

IN

ANAESTHESIA

Edited by

FRANKIS T EVANS

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and

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LONDON

BUTTERWORTH & CO (PUBLISHERS) LTD

1958

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MADE AND PRINTED IN GREAT BRITAIN BY
WILLIAM CLOWES AND SONS LIMITED
LONDON AND BECCLES

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PREFACE

MEDICINE has been called by Virgil a Quiet Art —yet so rapid has been its development of recent years that one may with justification wonder when is the opportunity of quietness presented The daily round the common task gives little chance for the practitioner in any branch to keep abreast of the phenomenal rate of expansion and accumulation of new knowledge, let alone to reflect in peace and quiet on the direction in which we are moving The average specialist can only manage to glance through the technical journals of his immediate interest and even this must be done at the end of a tiring and exacting day Recent technical advances however can seldom be safely practised without some knowledge of the basic facts upon which they are based and these are to be found dispersed throughout journals and volumes outside the usual field of reading of the clinician

In this book it has been our aim to present a review of new knowledge covering a wide area of theory as well as practice We have asked our authors also to scan the horizon for signs of the direction in which we are moving and to indicate the lines upon which we must work to advance further We had hoped that facts would be laced with a stimulating source of justifiable speculation and so put our readers in line with the most recent thoughts in this most absorbing field of medicine It is a first attempt to do this for anaesthesia in book form and, if we have only been partially successful, that is no fault of those who have contributed, the fault must be laid at our door and attributed to our inexperience in this, we believe, new type of review

Francis Bacon gave some good advice

> Reade not to contradict and confute Nor to Beleeve and Take for granted Nor to find Talke and Discourse But to weigh and Consider Some Bookes are to be Tasted Others to be Swallowed and Some Few to be Chewed and Digested

It is our hope that this volume might be counted worthy to be subjected to the latter treatment

Our thanks must be expressed to all those who have given up their valuable time to contribute to these pages to our Publishers for their patience, forbearance advice and criticism to Miss Finlayson, Secretary to the Department of Anaesthesia in the University of Liverpool for a deal of secretarial assistance with the manuscripts to those who have permitted us to reproduce illustrations from their pages, to whom we have made an acknowledgement in the captions

FRANKIS T EVANS
T CECIL GRAY

March 1958

CHAPTER 1

THE RELAXANT DRUGS

W. D. M. PATON

INTRODUCTION

THE MOST striking feature of the development of anaesthesia in the last twenty years has been the progressive assumption by the anaesthetist of responsibility for the control of functions of the body normally exerted by the body itself. Originally, anaesthesia did little more than produce unconsciousness with the resultant abolition of the sense of pain. But now the anaesthetist may breathe for a patient (having paralysed the muscles with relaxants), may control the patient's blood pressure (having paralysed the normal autonomic control), may control the body temperature (by artificial thermal exchange as well as by autonomically active drugs) and may even interfere quite substantially with the electrolyte balance of the *milieu interne*. The first step in this progressive mastering of the physiology of anaesthetized patients came when curare preparations were shown to be clinically useful in surgical anaesthesia. The success of such substances in rendering surgery quicker and more efficient has been a stimulus not only to the development of other relaxants, but to the closer study of their action and to a general interest by anaesthetists in using drugs.

THE MECHANISMS OF NEUROMUSCULAR TRANSMISSION

It is now generally accepted that transmission at the neuromuscular junction takes place by chemical means: that is, that a propagated impulse down a motor nerve causes the release at its terminations of acetylcholine, which then excites the specific receptor area underneath the nerve endings to elicit an "endplate potential"; this in turn excites the rest of the muscle fibre electrically. Recent electrophysiological work on the neuromuscular transmission has added some new interesting items of knowledge (*see* del Castillo and Katz, 1956, for a valuable review in which the principal references will be found).

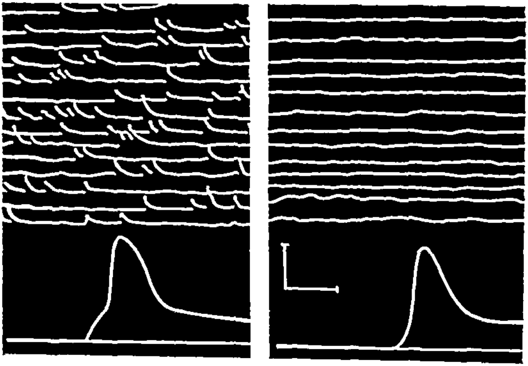
The nature of the change in the endplate membrane

Katz and his colleagues, in elegant experiments with micro-electrodes, have shown that acetylcholine produces at the endplate receptors a particular type of change of membrane permeability. They describe it as being equivalent to a "short circuit"; they mean by this that there is no *specific* increase in permeability to the ions either side of the membrane but that, so far as they could detect, the membrane becomes permeable to all ions indifferently. If this happens at a membrane then

cord which activates motoneurones (Eccles 1957) although we know that it is not acetylcholine

The site of acetylcholine receptors

Del Castillo and Katz using micro injection techniques have also proved that the receptors for acetylcholine are only on the outside of the endplate membrane They used micro-electrodes filled with acetylcholine from which brief pulses of acetylcholine could be discharged by passing current through the electrode and they recorded the effect by means of intracellular electrodes They found that typical endplate potentials can be produced more and more readily as the *syringe approached the endplate membrane until the point at which the* membrane was actually penetrated From this point onwards acetylcholine was neither effective itself nor did it modify the effect of acetylcholine administered



(*a*) (*b*)

FIG 2 —Spontaneous miniature endplate potentials in frog muscle intracellular recording In (*a*) the micro-electrode was inside the muscle fibre at the endplate region in (*b*) 2 millimetres away in the same fibre The upper part of (*a*) shows the miniature endplate potentials recorded at high amplification and slow speed (calibration 3 6 mV and 47 msec) the lower part the response to a nerve impulse at low amplification and higher speed (calibration 50 mV and 2 msec) The responses in (*b*) recorded in the same way show that the miniature endplate potentials are hardly detectable 2 millimetres away from the endplate and also show the pure muscle action potential delayed by propagation from the endplate 2 millimetres away

(*After Fatt and Katz (1952) by courtesy of J Physiol*)

from the outside This means that the receptors on which acetylcholine acts are only on the outer side of the membrane It renders highly improbable a theory which postulates any action for acetylcholine within the muscle fibre so far as changes in membrane potential are concerned

the potential which will come to be recorded across it will be that seen when two solutions of the same compositions as the extracellular and intracellular fluids come into contact This so called junctional potential is fairly small (not more than 15 mV, inside negative) Whenever acetylcholine acts at the endplate, therefore, it will by means of this short circuit action, tend to pull the membrane potential to this level Thus, when it acts on a resting muscle fibre, the endplate region is depolarized, that is it becomes negative relative to the rest of the fibre, and excites it But an even more interesting effect can be produced (Fig 1) Suppose that the fibre is excited by stimulating the muscle directly, away from the

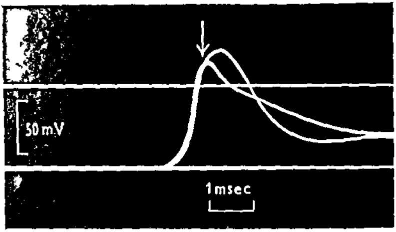


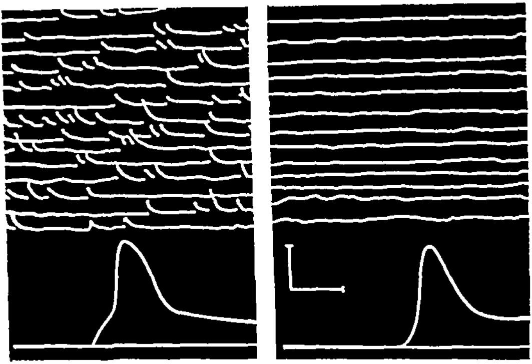
FIG 1 —Effect of the transmitter released during a directly excited muscle action potential Intracellular recording from endplate of frog s sartorius Temperature 19 C The larger of the two records is a simple *M* spike Arrow indicates commencement of *N* response just before the crest of the *M* spike Upper horizontal trace zero membrane potential lower horizontal trace resting membrane potential
(After del Castillo and Katz (1954b) by courtesy of J Physiol)

endplate (*M* response) Then an action potential will sweep over the endplate region and the usual overshoot of membrane potential (due to the very high sodium permeability during the action potential) will be seen Now suppose further that we time a shock to the nerve (*N* response) so that endplate activation by released acetylcholine coincides with the passage of the directly stimulated action potential Again acetylcholine s action is to short circuit the membrane, but now it shows itself by cutting down the overshoot tending again to pull the membrane to the junctional potential—this time from the opposite direction This work has been supplemented by the remarkable observation that the transmitter will produce its effect even in the absence of any standing resting potential across the membrane If a muscle is soaked in potassium sulphate (which completely depolarizes it) action of the transmitter can still be shown by the fall in membrane resistance which it elicits It seem therefore that the action of acetylcholine, and drugs like it at the motor endplate consists of a generalized increase in permeability which does not depend on any other particular ions being present nor even on a membrane potential being present It is interesting that an action of the same sort seems to be exerted by the chemical transmitter in the spinal

cord which activates motoneurones (Eccles 1957) although we know that it is not acetylcholine

The site of acetylcholine receptors

Del Castillo and Katz using micro injection techniques have also proved that the receptors for acetylcholine are only on the outside of the endplate membrane They used micro-electrodes filled with acetylcholine from which brief pulses of acetylcholine could be discharged by passing current through the electrode and they recorded the effect by means of intracellular electrodes They found that typical endplate potentials can be produced more and more readily as the syringe approached the endplate membrane, until the point at which the membrane was actually penetrated From this point onwards acetylcholine was neither effective itself nor did it modify the effect of acetylcholine administered



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They have extended this work (del Castillo and Katz 1957) to show that the receptors for *d*-tubocurarine decamethonium and suxamethonium occupy the same external site as those for acetylcholine, and have compared on frog muscle the actions of these agents

The quantal behaviour of the motor nerve endings

When Fatt and Katz first came to penetrate with micro electrodes the endplate region they found that even when the nerve was not being stimulated the membrane was not completely quiescent, but was the site of continuous small fluctuations of potential (Fig 2) These potential changes resembled miniature endplate potentials being of the same shape but about 1 per cent of the normal

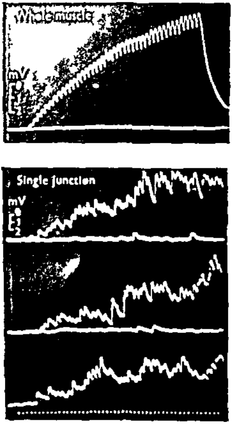

Fig 3 —Records from whole muscle (*above*) and from a single fibre with intracellular electrode (*below*) after treating preparation with solutions of raised magnesium and reduced calcium content during stimulation of the nerve at 100/sec In the record from the whole muscle the responses from some hundreds of end plates are averaged *But in the record from* a single fibre the quantal make up of the response can be seen The horizontal traces are taken in the resting state (note miniature potentials occasionally) the nerve stimuli are indicated by dots
(After del Castillo and Katz (1954a) by courtesy of J Physiol)

endplate potential Further it was found that these miniature endplate potentials were always quantal that is of a particular size or some higher multiple of that size, the quanta often being superimposed obviously one on another By calculating the electrical charge which was associated with these potential changes and on other grounds it was concluded that they could be produced only by many thousands of molecules of acetylcholine and not by single molecules Thus far of course the miniature endplate potentials might not necessarily bear any important relationship to normal transmission With the ordinary full sized endplate potential resulting from nervous excitation the potential change is so large that *even if individual miniature potentials are involved, they could not be*

identified But if neuromuscular transmission is impaired by raising the magnesium and diminishing the calcium of the surrounding fluid, then the endplate potential can be progressively reduced until it can be seen to be fragmented and to be built up of miniature units quanta comparable to those seen during the spontaneous activity just described (Fig 3)

This is important for the theory of acetylcholine release It had usually been supposed that the acetylcholine was in some way mobilized at the nerve ending and then diffused molecule by molecule out of the nerve endings towards the receptor area On the contrary it appears that the acetylcholine must be aggregated in packets in the nerve ending and that it is these packets which escape from the nerve ending there presumably breaking up and producing the discrete changes

FIG 4—Electron micrographs of a reptilian neuromuscular junction The nerve ending indents the sarcoplasm and fine junctional folds project from it The ending contains in addition to mitochondria (large dark particles) many small globules less than 0 1μ in diameter

(After Robertson cited by del Castillo and Katz (1956) by courtesy of Pergamon Press)

of endplate activity just described It is interesting that electron microphotographs of the nerve terminals show, in addition to mitochondria a mass of small vesicles which might be imagined each to contain the acetylcholine packet postulated (Fig 4) The practical implication of this of course has still to emerge although drugs active against acetylcholine release are known they are not yet of any obvious use But it makes all the difference to theories of acetylcholine release whether it is to be conceived as diffusing out of a transiently permeable membrane or as a process whereby relatively large conglomerates must be allowed to escape

The existence of spontaneous activity at the nerve endings (which occurs in

mammalian muscle also) (Boyd and Martin, 1956a) has the further consequence that the endplate is probably never at complete rest even when tonic motor nerve activity is absent. The frequency of the miniature endplate potential discharge can be increased by previous tetanization of the nerve, by raised osmotic pressure of the fluid surrounding it, or by potassium, it is decreased by cold and by botulinum toxin. The size of the endplate potentials is raised only by anti-cholinesterase drugs: nothing else has been found to increase the effectiveness of the quanta of acetylcholine released. Correspondingly, a dose of a competitive blocking agent will reduce or abolish the size of the miniature potentials.

MECHANISMS OF NEUROMUSCULAR BLOCK

The interest taken in muscle relaxants, and the occurrence of rather puzzling situations after anaesthesia, have led to a good deal of speculation. It is worth recapitulating the basic features of neuromuscular block, although these have been fully described many times (*see* Foldes, 1957, for a recent review). In neuromuscular block firstly nervous transmission, and secondly muscular excitability and force are intact. This may seem almost too elementary to mention. But in fact many cases of apnoea after surgical operation are attributed to the action of a muscle relaxant without any test whether central nervous activity, nervous conduction or muscular power are impaired. Classical curare-like action is associated, thirdly with a normal release of acetylcholine. There do not appear, as a matter of fact, to be any clinical situations outside botulism in which a depression of acetylcholine release might be anticipated. But drugs are being discovered which interfere with acetylcholine synthesis (and hence with acetylcholine release) so that this will become an important distinguishing feature. These three criteria suffice to characterize the classical agents like *d*-tubocurarine and the alkaloids from calabash curare.

But the situation is different with drugs like decamethonium and suxamethonium. The classical requirements are still fulfilled, but when the action of the drugs is probed it is found that they imitate the transmitter at the motor endplate. Thus, twitch of a mammalian muscle, the specific endplate depolarization, and the classical contracture of frog, avian and denervated muscle can all be produced. It may then be asked how neuromuscular block can be brought about. Argument proceeds about this (Foldes 1957) and the writer wishes here only to emphasize one change which it is known takes place in the muscle fibre, but does not occur in the muscle under *d*-tubocurarine: this is the development of electrical inexcitability of the endplate region and its immediate surroundings. Fig. 5 shows measurements of the excitability of the endplate region under these conditions: the stimulus required to produce excitation by means of two closely spaced electrodes increases something like 25 times after the action of decamethonium. Burns and Paton (1951) concluded that this inexcitability was a direct result of endplate depolarization and attributed it to an escape of potassium through the reduction of the membrane potential at this point. Whatever may be said about the fluctuations of membrane potential in this vicinity the fact that the membrane has become less excitable means that an endplate potential set up in this region must be larger than in the curarized muscle if it is to excite the rest of the muscle fibre. In other words, transmission is going to fail with relatively large endplate potentials

capable of exciting the normal muscle This in itself is sufficient to account for the neuromuscular blocking action possessed by the compounds It also accounts for the characteristic transience of the excitatory phenomena produced by drugs of this sort It is a curious fact that, by injecting a depolarizing drug, a standing depolarization at the endplate is produced which, other things being equal, would be sufficient to throw the muscle fibre into a violent tetanus It is only because the endplate region becomes less excitable that the muscle is protected from this presumably highly unphysiological and potentially exhausting state Fig 6 illustrates graphically the sort of sequence of events which one would reconstruct from the information available on mammalian muscles (Boyd and Martin, 1956b

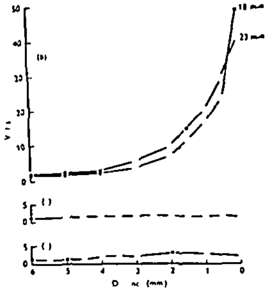

FIG 5 —Cat chloralose gracilis Graph of excitability measurements in (*a*) normal muscle (*b*) 18 and 23 min after 80 µg/kg decamethonium intravenously (*c*) after 0 7 mg/kg *d* tubocurarine intravenously Ordinates volts required to produce standard action potential by direct stimulation Abscissae distance along muscle fibre of point of stimulation from centre of endplate zone at zero

(After Burns and Paton (1951) by courtesy of J Physiol)

Burns and Paton 1951) The writer believes that these are the principal mechanisms involved in the ordinary use of drugs of this type, some special conditions are discussed below It may be noted that the fundamental cause of neuromuscular block by a depolarizing drug is not the depolarization itself (which would assist transmission) but the electrical inexcitability of the muscle resulting from it In many respects the change of excitability of the muscle is a better sign of the nature of the block than a measure of the standing depolarization

Accommodation to transmitter action

Although repeated cycles of paralysis and recovery can be produced with decamethonium or suxamethonium, it was early noticed that the depolarization produced in cat s gracilis muscle by successive doses dwindled somewhat (Burns and Paton 1951) A similar phenomenon was seen in the depolarization of muscles produced by large doses of an anticholinesterase (TEPP) (Douglas and Paton 1954) this may contribute to the resistance to cholinesterase poisoning described for certain phosphorus compounds if an animal could be brought through a first poisoning it was partially resistant to further doses (Barnes 1953) A diminishing action by acetylcholine was also described on frog muscle (Fatt 1950) In these instances, however, endplate depolarization never disappeared

mammalian muscle also) (Boyd and Martin, 1956a) has the further consequence that the endplate is probably never at complete rest even when tonic motor nerve activity is absent The frequency of the miniature endplate potential discharge can be increased by previous tetanization of the nerve, by raised osmotic pressure of the fluid surrounding it, or by potassium, it is decreased by cold and by botulinum toxin The size of the endplate potentials is raised only by anti cholinesterase drugs nothing else has been found to increase the effectiveness of the quanta of acetylcholine released Correspondingly, a dose of a competitive blocking agent will reduce or abolish the size of the miniature potentials

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by them not only dwindles but may totally disappear The muscle now cannot be excited through its nerve nor by added acetylcholine nor will anticholinesterases restore transmission He was able to demonstrate in rat muscle a similar phenomenon, although the endplate depolarization never sank below 30 per cent of its initial value If the acetylcholine is washed out the muscle fairly slowly recovers its normal response to acetylcholine Thesleff believes that his results show that acetylcholine and other depolarizing drugs exert a curare like action Zaimis (1953) has made a similar proposal, in applying her work to the genesis of myasthenia suggesting that in these patients acetylcholine released at motor nerves may come to have a dual action, first stimulating then blocking itself

Churchill Davidson and Richardson (1957) have put forward similar ideas on the basis of their work analysing the action of decamethonium and anti cholinesterases in myasthenic patients They noticed that a myasthenic patient deteriorated markedly whenever anticholinesterase therapy was continued but improved under conditions of rest and withdrawal of anticholinesterase therapy, when anticholinesterases would become temporarily effective again From observa tions such as this they concluded that her motor endplates were becoming resistant to acetylcholine (or its breakdown products) in proportion to the amount of acetylcholine released in their vicinity If this was the case then her condition should be improved by resting the endplate from its chemical stimulation *completely They attempted to do this by curarizing her with d tubocurarine for* 8 days Interestingly enough her requirement for *d* tubocurarine to produce a satisfactory degree of general neuromuscular block was in the normal range At the end of this rest period, and after an interval during which the effects of the *d* tubocurarine wore off the patient returned to a stronger state than earlier When anticholinesterases were administered, there was a dramatically satisfactory response, and for a period of several months she was stronger than she had been for a long time This is only one case, but so far as it goes it bears out to the full the idea that in myasthenics at least the motor endplates can become refractory *in one way or another as a result of continued exposure to acetylcholine so that* a possible method of treatment is to diminish such exposure

The writer finds the idea that acetylcholine can curarize the endplate a difficult concept, for two reasons The first is the remoteness in structure between ordinary curarizing drugs and acetylcholine All the active curare like compounds have relatively large molecules and simpler analogues are usually much less effective thus as an agent expected to imitate for instance, *d* tubocurarine, acetylcholine is structurally improbable Secondly, it seems unlikely that acetylcholine, acting at a site peculiarly rich in the enzyme specifically destroying it, could persist there after washing out, *in the way required to block receptors For this to occur* would imply a combination with receptors unlike the normal combination, and of a type which dissociated extraordinarily slowly Grob Johns and Harvey (1956) find that in the myasthenic the response to choline is also changed, and this substance normally depolarizing ' in type comes to have an apparently competitive action This would allow one to argue that it is choline rather than acetylcholine which may persist at the receptors and cause block The main difficulty is that choline is about 1,000 times less active than acetylcholine, and it is doubtful whether enough choline would appear to exert a significant effect The writer feels, therefore, that the change in response of the *endplate to acetylcholine*

and the appearance was that of a depolarizing agent becoming less effective, rather than that of its action changing qualitatively

Somewhat different was the phenomenon demonstrated by Zaimis (1953) On some muscles for example of monkey, decamethonium on its first administration would have its usual action, but as doses were repeated it became less active, and came to exert actions very like those seen with *d* tubocurarine This could be detected even in the cat if the soleus muscle was studied These results were very similar to those found by Paton and Perry (1953) with nicotine on autonomic ganglia In this case nicotine starts by exciting ganglia, with a well marked

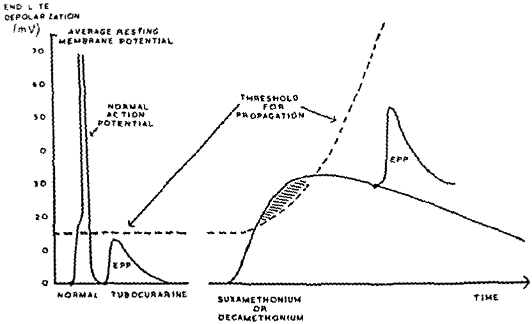

FIG 6—Diagram of neuromuscular transmission and block Under normal conditions a nerve stimulus gives rise to an endplate depolarization when this exceeds the threshold for exciting the muscle fibre a propagated action potential arises from it After tubocurarine in sufficient dose the endplate depolarization does not reach the threshold required for propagation and a pure endplate potential (EPP) is seen After decamethonium or suxamethonium the endplate is depolarized by the drug and this depolarization may rise above the threshold But the threshold for propagation also rises cutting short the period over which the muscle can show stimulant effects (hatched area) If the nerve is stimulated now an endplate potential large enough to excite under normal conditions can be obtained it is ineffective because of the rise in threshold

depolarization but presently the excitant depolarizing action disappears totally, and although complete block may persist it is now of a hexamethonium type A similar sequence has been observed with decyltrimethylammonium on the motor endplate Here we seem to have unequivocal evidence of a change in the character of the block not merely of the intensity of action

Recently Thesleff (1955 1956) using micro electrodes for internal recording of membrane potentials of frog muscles *in vitro* made the remarkable observation that if the muscle is exposed to depolarizing drugs including acetylcholine itself for a sufficient period (15 minutes or more) the endplate depolarization produced

by them not only dwindles but may totally disappear The muscle now cannot be excited through its nerve nor by added acetylcholine nor will anticholinesterases restore transmission He was able to demonstrate, in rat muscle, a similar phenomenon although the endplate depolarization never sank below 30 per cent of its initial value If the acetylcholine is washed out the muscle fairly slowly recovers its normal response to acetylcholine Thesleff believes that his results show that acetylcholine and other depolarizing drugs exert a curare like action Zaimis (1953) has made a similar proposal, in applying her work to the genesis of myasthenia, suggesting that in these patients acetylcholine released at motor nerves may come to have a dual action, first stimulating then blocking itself

Churchill Davidson and Richardson (1957) have put forward similar ideas on the basis of their work analysing the action of decamethonium and anticholinesterases in myasthenic patients They noticed that a myasthenic patient deteriorated markedly whenever anticholinesterase therapy was continued, but improved under conditions of rest and withdrawal of anticholinesterase therapy when anticholinesterases would become temporarily effective again From observations such as this they concluded that her motor endplates were becoming resistant to acetylcholine (or its breakdown products) in proportion to the amount of acetylcholine released in their vicinity If this was the case then her condition should be improved by resting the endplate from its chemical stimulation completely They attempted to do this by curarizing her with *d* tubocurarine for 8 days Interestingly enough her requirement for *d* tubocurarine to produce a satisfactory degree of general neuromuscular block was in the normal range At the end of this rest period, and after an interval during which the effects of the *d* tubocurarine wore off, the patient returned to a stronger state than earlier When anticholinesterases were administered, there was a dramatically satisfactory response, and for a period of several months she was stronger than she had been for a long time This is only one case but so far as it goes it bears out to the full the idea that in myasthenics at least the motor endplates can become refractory in one way or another as a result of continued exposure to acetylcholine, so that a possible method of treatment is to diminish such exposure

The writer finds the idea that acetylcholine can curarize the endplate a difficult concept for two reasons The first is the remoteness in structure between ordinary curarizing drugs and acetylcholine All the active curare like compounds have relatively large molecules and simpler analogues are usually much less effective thus as an agent expected to imitate for instance, *d* tubocurarine, acetylcholine is structurally improbable Secondly, it seems unlikely that acetylcholine acting at a site peculiarly rich in the enzyme specifically destroying it could persist there after washing out, in the way required to block receptors For this to occur would imply a combination with receptors unlike the normal combination, and of a type which dissociated extraordinarily slowly Grob, Johns and Harvey (1956) find that in the myasthenic the response to choline is also changed and this substance normally depolarizing in type, comes to have an apparently "competitive action This would allow one to argue that it is choline, rather than acetylcholine which may persist at the receptors and cause block The main difficulty is that choline is about 1,000 times less active than acetylcholine, and it is doubtful whether enough choline would appear to exert a significant effect The writer feels therefore that the change in response of the endplate to acetylcholine

which occurs in myasthenia and in various experimental conditions may be better regarded not as a curarization but as a developing refractoriness or accommodation of the receptors, comparable perhaps to the process which leads to 'inactivation of the sodium pump' if an excitable membrane is held in the depolarized state

The application of this work to clinical practice is still to come It seems to be implied that a depolarizing drug may produce, in occasional patients or under particular conditions, one of two states, either one in which it is behaving like decamethonium does in the monkey in which cases anticholinesterases may be helpful or one in which the endplates have become so refractory that acetylcholine itself produces further neuromuscular block, in which cases anticholinesterases may actually make things worse It remains for the application of electro physiological techniques to patients under anaesthesia to discover what in fact happens and, no doubt to reveal still other influences at work

THE SMALL MOTOR NERVE FIBRE SYSTEM

It has recently been realized that voluntary movement is controlled to a very important degree by the activity of the small motor nerve fibre system (*see* Hammond Merton and Sutton, 1956, for a discussion) This system consists peripherally of small myelinated fibres (often called *gamma* fibres in contrast to the *alpha* fibres innervating voluntary muscle itself), which leave the spinal cord in the ventral roots and innervate the contractile substance of the muscle spindles (Fig 7) In so doing they 'bias' the muscle spindles, so that their sensory discharge to extension of the muscle occurs more readily, and is more vigorous for a given extension If there is an intact stretch reflex, so that a reflex motor discharge occurs when the muscle spindles send in their afferent signals then it is possible that muscular movement might be brought about entirely by the small motor nerve fibre system Thus if they become active the afferent inflow would increase and reflexly the large motor nerve fibres would fire producing a movement This may seem a roundabout way of producing a muscular movement but it has many of the advantages possessed by a servo mechanism in respect of producing controlled activity in the muscle The importance of this pathway has become clear from work on the central nervous system which shows for instance that one of the tasks of the cerebellum is to control how far activity is mediated by this servo mechanism and how far movements directly through the voluntary motor nerve fibre system are produced (Fig 8) The two types of movement have rather different characteristics That controlled by the small motor (*gamma*) fibres is essentially directed at controlling the length of the muscle for the muscle spindles register, not tension but any disparity between the length of the fibres they are imbedded in and their own length Direct (*alpha*) activity on the other hand simply results in muscle tension of a given magnitude The difference between the two pathways can be seen by the result of lesions of the cerebellum in which the force of muscular movement may not be much reduced but the movements are characteristically clumsy as though the ability to control position (that is the length at which the muscle is acting) is impaired

The relevance of this to anaesthesia lies in the fact that the small motor nerve fibre system, like that of the motor fibres to the muscles is a cholinergic one

This means that any drug which can paralyse the neuromuscular junction will also interfere with the effect of the *gamma* fibres on the muscle spindles A paralysis of the *gamma* fibre neuromuscular junction will have as one major consequence a reduction of the afferent proprioceptive inflow from the muscle spindles It is already known that selective paralysis by procaine of the *gamma* fibres in the sciatic nerve of an animal with decerebrate rigidity will produce substantial changes in the stretch reflex (Matthews and Rushworth, 1957)

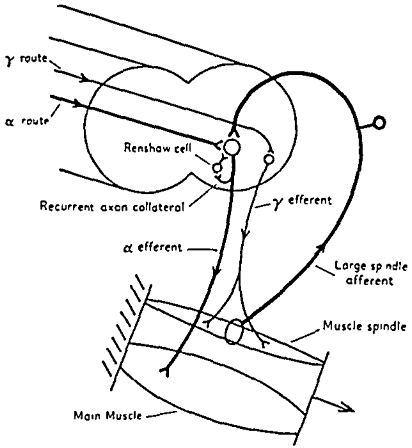

FIG 7 —Diagram of stretch reflex and related mechanisms The muscle spindle lies in parallel with the main muscle and its fast-conducting afferent is in synaptic connexion with the large α motoneurone supplying the main muscle fibres A slow conducting γ motor efferent (thin line) supplies the contractile poles of the spindle and thus can alter the bias on the spindle sensory ending

The muscle can be made to contract either by impulses from higher centres exciting the α motoneurone direct (the α route) or by impulses in the γ-efferents (the γ route) which activate the muscle indirectly *via* the stretch reflex arc (the follow up servo)

A subsidiary feedback loop *via* the recurrent axon collateral and an inhibitory Renshaw interneurone may be concerned in stabilizing the response of the α motoneurone to its excitatory input

(After Hammond Merton and Sutton (1956) by courtesy of B it med Bull)

In the anaesthetized patient then, the proprioceptive inflow will be considerably reduced when he is receiving *d* tubocurarine On the other hand, if a depolarizing drug is given one would anticipate that for a period at least the muscle spindle afferent discharge would be considerably enhanced, and in animals muscle spindle firing after suxamethonium has actually been shown (Granit, Skoglund and Thesleff 1953) There has always been some uncertainty as to the origin of the vigorous fasciculations seen when a depolarizing drug is injected The muscular

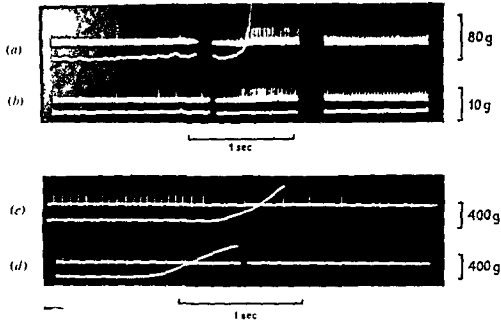

FIG 8 — Muscular contractions initiated *via* the follow up servo and *via* the direct route In these experiments on decerebrate cats contraction of the ankle extensors is induced reflexly by moving the head up and down Muscle tension is recorded (continuous line) together with the spike discharge from a single muscle spindle The interruption of the traces in (*a*) and (*b*) signals the time of head movement but was late in (*d*)

(*a*) (*b*) decerebration by intercollicular section
(*a*) muscle contraction accompanied by great acceleration of spindle discharge indicating that the follow up servo (γ route) is activated
(*b*) this is confirmed after cutting the dorsal roots when spindle acceleration occurs as before but there is no contraction visible even with the greater sensitivity of the myograph
(*c*) (*d*) in other cat decerebrated by tying the basilar artery This also kills the anterior lobe of the cerebellum and favours the direct (α route) of excitation
(*c*) contraction is not accompanied by spindle acceleration
(*d*) after cutting dorsal roots contraction occurs as before The α motoneurones are no longer dependent on spindle drive

After Eldred, Granit and Merton (1953), Granit, Holmgren and Merton (1955), Hammond, Merton and Sutton (1956) by permission of J Physiol and Brit med Bull)

twitches observed are much too vigorous to be due to the activation of single muscle fibres A second possibility is that a sort of axone reflex might be set up in which depolarization at a motor endplate also depolarizes the motor nerve terminals and causes an antidromic discharge which then by an axone reflex fires off the motor axones belonging to the same motor unit Unfortunately there is no clear evidence that such an axone reflex occurs Consequently the third possibility is also worth bearing in mind that the fasciculations are mediated by an action of the drug on muscle spindles causing an increased afferent discharge leading to local motor contractions reflexly initiated

Besides being relevant to the peripheral fasciculations the action of relaxants on the *gamma* system will also influence peripheral muscle tone. One normally supposes that the reduction of tone seen in anaesthesia is due to the neuromuscular blocking action of the drugs employed, but it might to a significant degree also be due to the removal of *gamma* fibre activation of the muscle spindles producing a reduction of tone not unlike that produced by section of dorsal roots. Such an action would have analogies with the reduction of tone by some central depressants when they abolish the stretch reflex without necessarily having any peripheral neuromuscular action. Finally, it is worth bearing in mind that the mere reduction of proprioceptive flow to the brain stem may have more subtle effects. Experiments by Bremer and his school (Bremer, 1953) have shown that if a cat's brain is sectioned at about the junction between the mesencephalon and the diencephalon (*cerveau isolé*) so that all the sensory inflow except that from the eyes and nose, is removed (that is, all the inflow from the spinal cord and especially that from the trigeminal nerve), then the forepart of the brain falls into a state indistinguishable from sleep. A section placed a little more posteriorly (*encephale isolé*), so that the trigeminal nerve is active, gives signs of wakefulness. This is a reminder of how far afferent inflow determines states of sleep. It makes it a possibility that, by the action of a relaxant paralysing the *gamma* fibres and so reducing muscle spindle discharge a reduction of proprioceptive inflow to the higher centres might actually contribute to a prolonged sleep like state. Although true central actions by muscle relaxants are, in the writer's opinion, rather improbable by virtue of the great efficiency of the blood brain barrier, indirect actions of this sort deserve serious consideration.

CONCLUSION

Since they were first discovered, curare and substances like it have not failed to present intriguing problems. No attempt has been made in this review to survey the numerous investigations made into the factors which modify the effect and duration of these drugs. It is hoped however that some idea has been conveyed of the fields still to be developed: the intimate details of receptor action, the ionic changes associated with it, the applied pharmacology of the small motor nerve fibre and muscle spindle and the whole of human neuromuscular pharmacology and physiology: all these open up fascinating vistas for exploration by laboratory worker and clinician alike.

REFERENCES

Barnes J M (1953) *Brit J Pharmacol* 8 208
Boyd I A and Martin A R (1956a) *J Physiol* 132 61
— — (1956b) *Ibid* 132 74
Bremer F (1953) *Some Problems in Neurophysiology* London Athlone Press
Burns B D and Paton W D M (1951) *J Physiol* 115 41
Churchill Davidson H C and Richardson A T (1957) *Lancet* 1 1221
del Castillo J and Katz B (1954a) *J Physiol* 124 574
— — (1954b) *Ibid* 125 546
— — (1956) *Progr Biophys* 6 121
— — (1957) *Proc roy Soc B* 146 339 357
Douglas W W and Paton W D M (1954) *J Physiol* 124 325

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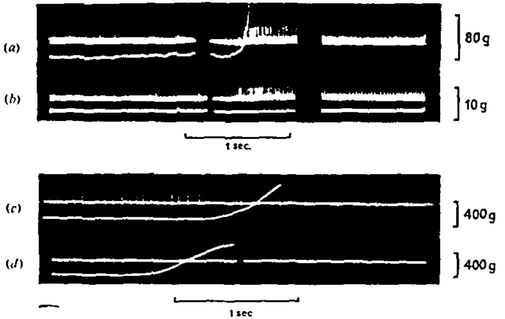

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CHAPTER 2

PHARMACOLOGY OF NEW DRUGS

J W DUNDEE

AT THE END of the first century of the use of surgical anaesthesia the anaesthetist had at his disposal at least one representative of each of the major groups of narcotic drugs and adjuvants During the last decade no new group of narcotics has come into routine use although the ganglion blocking drugs have been introduced The new developments have been mostly concerned with the adjuvants (muscle relaxants analgesics and hypotensive agents), which are outside the scope of this chapter, and also with modifications of anaesthetic techniques using drugs already established

Many new agents have been subjected to clinical trials within the past few years and the reasons for their introduction and their place in the future can best be appreciated if the present day trends in anaesthetic technique are first discussed

(1) Use of non inflammable agents Despite recent advances in operating theatre and anaesthetic equipment, explosions still occur periodically and with the increasing use of electrocautery, it is appreciated that complete safety can be achieved only by the elimination of inflammable agents

(2) Employment of lighter planes of anaesthesia and more use of analgesics There is an ever increasing accumulation of evidence to condemn the view that deep anaesthesia is essential to eliminate noxious stimuli from the site of operation

(3) Minute to minute control of the degree of depression and selective control of the various conditions which constitute the state of anaesthesia This necessitates the use of shorter acting and more controllable agents Here most of the advances have been made outside the field of the anaesthetic agents *per se* Examples are the introduction of l noradrenaline suxamethonium, alphaprodine and tri metaphan (Arfonad) The modern trend is a search for the ideal anaesthetic combination of non toxic short acting agents rather than for the ideal anaesthetic agent

ETHERS

Although diethyl ether has been in clinical use for over a century, it is still unrivalled as the anaesthetic ether preferred by the great majority of anaesthetists all over the world Apart from the divinyl compound which is used mainly as an induction agent or for minor procedures where the irritant effect and slower action of diethyl ether are disadvantageous, no other ether has found wide acceptance

Most of the recent work in this subject is the result of the systematic study of various ethers with anaesthetic action by John C Krantz Jr and his colleagues

Eccles J C (1957) *The Physiology of Nerve Cells* London Oxford University Press
Fatt P (1950) *J Physiol* **111** 408
— and Katz, B (1952) *Ibid* **117** 109
Foldes F (1957) *Muscle Relaxants in Anesthesiology* Springfield Thomas
Granit R Skoglund S and Thesleff S (1953) *Acta physiol scand* **28** 134
Grob D Johns R J and Harvey A M (1956) *Johns Hopk Hosp Bull* **99** 136
Hammond P H Merton P A and Sutton G G (1956) *Brit med Bull* **12** 214
Matthews P B E and Rushworth G (1957) *J Physiol* **135** 245 263
Paton W D M and Perry W L M (1953) *J Physiol* **119** 43
Thesleff S (1955) *Acta physiol scand* **34** 218 386
— (1956) *Ibid* **37** 330
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Thesleff S (1955) *Acta physiol scand* **34** 218 386
— (1956) *Ibid* **37** 330
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TABLE I

IMPORTANT PROPERTIES OF NEW AND ESTABLISHED VOLATILE ANAESTHETIC AGENTS

Prepared from data by Adriani (1952), Sadove and his colleagues (1955, 1956), Raventos (1956) and Dundee, Linde and Dripps (1957)

	ETHERS					HALOGENATED HYDROCARBONS			
Drug	*Diethyl*	*Divinyl*	*Methyl n propyl*	*Ethyl vinyl*	*Trifluoroethyl vinyl*	*Trichlorethylene*	*Halothane*	*Chloroform*	*Ethyl Chloride*
Trade names		*Vinesthene* *Vinethene*	*Neothyl* *Metropyl*	*Vinamar*	*Fluoromar*	*Trilene* *Trimar*	*Fluothane*		*Narcotile*
Formula	CH_3CH_2 >O CH_3CH_2	$CH_2=CH$ >O $CH_2=CH$	CH_3 >O $CH_3CH_2CH_2$	CH_3CH_2 O $CH_2=CH$	CF_3CH_2 >O $CH_2=CH$	H Cl / Cl—C=C—Cl	F Br / F—C—C—Cl / F H	$CHCl_3$	C_2H_5Cl
Boiling point °C	34.6	28.4	39.0	35.8	42.7	87.0	50.2	61.[illegible]	1[illegible]
Specific gravity (20° C)	0.71	0.77	0.73	0.76	1.13	1.47	1.86	1.49	0.91
Calculated gas density (cf air=1)	2.6	2.4	2.6	2.5	4.4	4.5		4.[illegible]	[illegible]
Vapour pressure mm Hg at 20° C	442	553	442	428	295		243	160.5	
at 40° C	921	1145	921		670				
Inflammability range in air	1.8–36.5	1.7–27.0	1.8–36.5		4.0*	—		—	3.8–11.8
in oxygen	2.1–82.5	1.8–85.5	2.1–82.5	2.1*	4.2*	—	—	—	4.0–67.2
in nitrous oxide-oxygen	1.5–24.2	1.4–24.8	1.5–24.2		4.0*	—	—	—	
Concentrations for surgical anaesthesia Inhaled gas (vols/100 ml)	3–10	4–12		4	3.8	1.5	1.3	1.2	3.45
Blood (mg/100 ml)	50–150	30–40		about 25	10–40	6–12		25–70	20–30
Solubility in water µl/100 ml	8.0	0.7		0.8	0.4		0.34	0.8[illegible]	0.5[illegible]
Oil/water solubility Partition coefficient	3.2 / 15.00	45 / 7.10	10	45	91 / 5.00	38.4	330	100	

* Lower limit

from the University of Maryland In 1946 Krantz and his co workers drew attention to methyl n propyl ether This drug has attracted attention from time to time but never achieved widespread popularity Krantz and his colleagues (1947) reported the anaesthetic action of ethyl vinyl ether, but its clinical use was not described until 1955 by Dornette and Orth and by Sadove Wyant and Cletcher Partially fluorinated ethers were studied by Lu, King and Krantz (1953) who suggested that trifluoroethyl vinyl ether gave promise of being a useful anaesthetic agent This drug was further investigated by Krantz and his colleagues (1953) and clinical reports on its use have been published by Sadove, Balagot and Linde (1956) Gainza and his colleagues (1956) and Dundee, Linde and Dripps (1957) This was the first fluorinated volatile drug to be introduced into anaesthesia

Before discussing the actions of these new ethers, in order that their value may be more rapidly assessed it seems advisable to review the aspects in which diethyl ether falls short of the ideal agent From the patient s point of view, the pungent odour and slow induction are the major drawbacks Irritation of the respiratory tract causes salivation and coughing during light anaesthesia In deeper planes hypotension is not uncommon and the peripheral vasodilatation places a burden on an unhealthy cardiovascular system which may be disastrous in severe peripheral circulatory failure Within the concentration used in clinical anaesthesia the vapour of ether is inflammable and explosive if mixed with oxygen or nitrous oxide and oxygen After prolonged deep anaesthesia the recovery of protective reflexes may be slow and nausea and vomiting are frequent and may be prolonged

The important physical properties of the new ethers are compared with those in current use in Table I Except for trifluoroethyl vinyl ether no ether shows any advantage over diethyl as regards inflammability Even this fluorinated compound is inflammable within most of the anaesthetic range although Sadove Balagot and Linde (1956) report that the minimum spark ignition energy for trifluoroethyl ether is higher than for other ethers

Ethyl vinyl ether (EVE)

Ethyl vinyl ether must not be confused with the mixture of ethyl and vinyl ethers (VAM) introduced by Bourne McDowell and Whyte (1937) although it is interesting to note that Leake and Chen (1930) mentioned a brief experiment with ethyl vinyl ether in their first paper on divinyl ether Ethyl vinyl ether is a clear colourless liquid with a very pungent odour not unlike that of diethyl ether The pure drug is unstable and 3 0 per cent ethyl alcohol and 0 01 per cent phenyl alpha naphthylamine are added in the commercial preparation to prevent polymerization, oxidation and aldehyde formation

As might be expected from the few published clinical reports it appears that the course of anaesthesia with ethyl vinyl ether is intermediate between that of diethyl and divinyl ether Induction is rapid but not so quick as with divinyl ether phenomena attributable to irritation of the tracheobronchial tree are seen less frequently than with diethyl ether although salivation is common Although anaesthesia can be deepened easily one is not as likely to produce apnoea inadvertently as with divinyl ether Dornette and Orth (1955) record a 1 6 per cent incidence of convulsions with ethyl vinyl ether as compared with 3 2 per cent abnormal muscle movements with divinyl ether reported by Di Giovanni and Dripps (1956)

morphine or pethidine Intercostal paralysis (plane 3 stage 3) may appear before complete cessation of eyeball movement or loss of the pharyngeal reflex (plane 3 stage 1) Although the electroencephalographic pattern of cerebral depression described for diethyl ether by Courtin and his colleagues (1950) is frequently seen during induction with trifluoroethyl vinyl ether, there is often difficulty in deter mining the depth of anaesthesia from the electroencephalographic tracing Generally speaking levels 2–3 indicate light surgical anaesthesia while apnoea appears between levels 5 and 7

One might expect from the presence of a halogen that trifluoroethyl vinyl ether would sensitize the heart to the effect of adrenaline, but in animals the opposite effect appears to occur and an injection of adrenaline has less effect on the electrocardiographic pattern during anaesthesia than in the conscious animal (Orth 1955 Gainza and his colleagues, 1956) Hypotension invariably occurs during deep trifluoroethyl vinyl ether anaesthesia and the frequency with which deep anaesthesia is inadvertently obtained may lead to a higher incidence than during the use of diethyl ether However, the blood pressure rapidly returns to normal when anaesthesia is lightened Apart from transient displacement of the pacemaker no cardiac irregularities have been reported during the use of trifluoroethyl vinyl ether In contrast with other ethers, effects on the blood pressure which are secondary to tachypnoea are not infrequent During a short period of increased respiratory rate there is a rise in blood pressure but if tachypnoea persists for longer than an hour hypotension invariably occurs, and this may persist into the post operative period

Trifluoroethyl vinyl ether appears to be a profound respiratory depressant in deeper planes of anaesthesia Tachypnoea frequently occurs in patients who are not given morphine or pethidine as pre operative medication The respiratory rate increases with the depth and duration of anaesthesia but established tachypnoea can be quickly reduced by the intravenous injection of 10–20 milligrams of pethidine Tidal volume is markedly depressed at high respiration rates and acidosis follows prolonged tachypnoea (Dundee and Dripps 1957)

Muscular relaxation is variable with trifluoroethyl vinyl ether, but difficulty in assessing the depth of anaesthesia may lead to poor operating conditions Like diethyl ether the drug seems to be synergistic with *d* tubocurarine chloride Recovery from anaesthesia is more rapid than after diethyl ether Reports of the incidence of post operative nausea and vomiting are variable (11–45 per cent) but in the absence of a controlled study it is not possible to say whether trifluoroethyl vinyl ether has any advantage over other ethers in this respect

Some increase in blood sugar after one hour of trifluoroethyl vinyl ether anaesthesia similar in extent to that observed during cyclopropane anaesthesia, has been reported by Gainza and his colleagues (1956) There is some increase in bleeding time Although an increase in bromsulphthalein retention during anaesthesia has been reported, Sadove Balagot and Linde (1956) consider that the effects of the drug on liver function compare favourably with those of ether and spinal anaesthesia

It can be seen that while the new ethers may have slight advantages over diethyl ether they are not such as will ensure them a lasting place in anaesthesia

The effects of ethyl vinyl ether on the cardiovascular system are similar to those of diethyl ether, circulatory depression occurring in a deep plane of anaesthesia In general this drug seems to share with other anaesthetic agents a tendency to displace the pacemaker during deep anaesthesia Premature auricular contractions have been observed during its use, but it does not apparently cause ventricular arrhythmias

Rapid emergence at the termination of anaesthesia with very early return of protective reflexes and consciousness is one of the advantages claimed for ethyl vinyl ether and this has proved valuable in dental anaesthesia (Sadove, Kowalski Balagot and Krol 1955) Nausea and vomiting are fairly common, and since divinyl ether is known to have a toxic effect on the liver after prolonged use (Goldschmidt and his colleagues 1934) this aspect of the use of ethyl vinyl ether has been extensively investigated However, repeated administration of the drug to healthy dogs had no effect on hepatic function (Dornette, Bragman and Orth, 1954) and in man the degree of impairment of bromsulphthalein excretion after ethyl vinyl ether compares favourably with that recorded after diethyl ether (Sadove Wyant and Cletcher, 1955) The drug has no serious effect on the blood but a moderate leucocytosis occurs in about one fifth of the patients Large doses of ethyl vinyl ether seem to predispose to temporary acetonuria

Trifluoroethyl vinyl ether

Trifluoroethyl vinyl ether is a clear colourless liquid with a pleasant odour which is less pungent than that of diethyl ether and resembles somewhat methyl n propyl ether The trifluorcarbon configuration is stable and the drug possesses the properties of inorganic fluorides There is no tendency for the vinyl group ing to hydrolyse at high temperatures and the drug can be safely used in a closed circuit with soda lime

The induction of anaesthesia is much smoother than with diethyl ether, but the high boiling point of the fluoro compound makes the use of the open drop technique difficult Although loss of consciousness is rapidly achieved with trifluoroethyl vinyl ether the onset of surgical anaesthesia may be somewhat prolonged During the induction period a very marked analgesia is present

Once the level of surgical anaesthesia has been achieved the control of the depth of anaesthesia is much more flexible with this agent than with its non fluorinated isomer or with diethyl ether In fact anaesthesia can be deepened or lightened with a rapidity which can be alarming and alert attention is needed during the administration In this respect as in others the drug resembles cyclo propane Anaesthesia can be achieved with a respired gas concentration of 3-12 9 vols per cent and the blood levels vary from 10 milligrams per cent in light anaesthesia to 40 milligrams per cent in the fourth plane of the third stage (Sadove, Balagot and Linde 1956 Dundee Linde and Dripps 1957) The ease with which the depth of anaesthesia can be varied with trifluoroethyl vinyl ether may in part account for the observation that jaw relaxation is less consistent during surgical anaesthesia than with diethyl ether A few breaths of air during laryngoscopy may lighten the anaesthesia to such a degree that intubation becomes difficult or impossible

The classical stages of ether anaesthesia as described by Guedel, are frequently inapplicable to trifluoroethyl vinyl ether especially after the pre operative use of

morphine or pethidine Intercostal paralysis (plane 3, stage 3) may appear before complete cessation of eyeball movement or loss of the pharyngeal reflex (plane 3 stage 1) Although the electroencephalographic pattern of cerebral depression described for diethyl ether by Courtin and his colleagues (1950) is frequently seen during induction with trifluoroethyl vinyl ether, there is often difficulty in determining the depth of anaesthesia from the electroencephalographic tracing Generally speaking levels 2–3 indicate light surgical anaesthesia while apnoea appears between levels 5 and 7

One might expect, from the presence of a halogen, that trifluoroethyl vinyl ether would sensitize the heart to the effect of adrenaline, but in animals the opposite effect appears to occur, and an injection of adrenaline has less effect on the electrocardiographic pattern during anaesthesia than in the conscious animal (Orth 1955 Gainza and his colleagues 1956) Hypotension invariably occurs during deep trifluoroethyl vinyl ether anaesthesia and the frequency with which deep anaesthesia is inadvertently obtained may lead to a higher incidence than during the use of diethyl ether However, the blood pressure rapidly returns to normal when anaesthesia is lightened Apart from transient displacement of the pacemaker, no cardiac irregularities have been reported during the use of trifluoroethyl vinyl ether In contrast with other ethers, effects on the blood pressure which are secondary to tachypnoea are not infrequent During a short period of increased respiratory rate there is a rise in blood pressure but if tachypnoea persists for longer than an hour hypotension invariably occurs, and this may persist into the post operative period

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Ether analgesia

A new approach is in the use of diethyl ether analgesia This can be accomplished with concentrations of the drug which are without any obvious effect on the cardiovascular system

As the result of a detailed study of the first stage of ether narcosis, Artusio (1954) has divided it into 3 planes In plane 3, which occurs just before the loss of consciousness, there is total analgesia and amnesia This plane has been used for operation on the mitral valve in 110 patients and in 25 other cases, including abdominal surgery (Artusio, 1955) Following a sleep dose of thiopentone nitrous oxide–oxygen–ether is administered until surgical anaesthesia is obtained After thorough application of a topical analgesic to the larynx intubation is performed Hyperventilation is then carried out with oxygen only until the patient is returned to the stage of consciousness Should a pain response be evoked more ether is added until total analgesia is obtained, the patient remaining conscious and co operative The average level of ether in the venous blood is 15 milligrams per cent in this plane of analgesia The absence of an excitement stage during the lightening of anaesthesia is very notable, and Artusio suggests that there is really no definitive second stage on a dose response basis, but that the delirium may be a result of a fear reaction to the initial loss of consciousness

Because of the narrow margin between partial analgesia and total analgesia the electroencephalographic pattern of the stage of ether analgesia has been studied in detail (Bellville and Artusio, 1955) The recording shows predominantly rhythmic, sinusoidal activity of 20 to 22 cycles per second with an amplitude of 30 to 40 microvolts By using the electroencephalogram as a monitor it is possible with the muscle relaxants to extend ether analgesia to operations requiring profound muscular relaxation

Although there are as yet few published reports on the use of ether analgesia it is possible that with this technique the response to stresses such as trauma or blood loss is minimal If this work is confirmed we may have a very valuable new application of a drug for which by virtue of its undesirable effects during surgical anaesthesia pharmacologists and anaesthetists have been looking for a more satisfactory substitute More important still we may have a new approach to the whole subject of surgical anaesthesia, in the light of which it may be necessary to re examine the effects of the established anaesthetic agents with special emphasis on their ability to produce total analgesia (Liang and Dodd 1956)

OTHER HALOGEN COMPOUNDS

Isopropyl chloride

Isopropyl chloride is a non irritant volatile compound having a potent anaesthetic action with a short induction period and rapid recovery Many of its actions resemble those of cyclopropane but several reports on its use (Cope 1950 Lockett 1951, Elam and Moorhouse 1951 Liang and Dodd 1956) have shown it to be too potent a myocardial poison to warrant its use in clinical anaesthesia Two cases of cardiac arrest have been described (Roualle 1950 and Macdonald 1950)

Halothane (Fluothane)

Halothane is the most promising of a series of fluorinated hydrocarbons synthesized by C W Suckling of Imperial Chemical Industries Ltd Its pharmacology was investigated by Raventos (1956) Halothane is a heavy colourless liquid with an odour which bears some similarity to that of both trichloroethylene and chloroform The drug decomposes slowly with the formation of volatile acids when exposed to light but is stable if stored in amber coloured bottles or if 0 01 per cent thymol is added The physical characteristics of halothane are shown in Table I, where it is compared with new and established volatile agents Stability in contact with soda lime permits the safe use of the drug in a closed circuit and in this respect it is superior to trichloroethylene

Experiments with mice showed halothane to be about five times as potent as diethyl ether (Raventos, 1956) In these animals it had an anaesthetic index (LC50/AC50) of 3 3 compared with 1 7 for ether, 1 5 for chloroform and cyclo propane and 5 0 for trichloroethylene Raventos reported a smooth induction of anaesthesia in animals with prompt recovery even after 5-6 hours of anaesthesia In view of the high oil/water partition coefficient this prompt recovery has been questioned by Burn and his colleagues (1957) They suggested that after prolonged administration a good deal of the drug would be absorbed by the fatty tissues, thus taking a considerable time for complete elimination Using the knee jerk as a criterion for recovery, these workers found that the duration of recovery depends both on the time of exposure and on the depth of anaesthesia Several clinical observations have been made which are in keeping with this latter view

In animals and man, halothane in concentrations up to 2 per cent causes little irritation to the tracheobronchial tree and the absence of secretions is a feature of the anaesthesia, as compared with other volatile agents Both the amplitude and frequency of respiration are decreased during anaesthesia with halothane When the respiration ceased in animals, the blood pressure was still reasonably high and the heart continued to beat for about nine to ten minutes (Raventos 1956) The degree of respiratory depression in man during surgical anaesthesia of moderate depth is such that cyanosis frequently occurs when the halothane is volatilized with air As is to be expected, the depression of respiratory minute volume is more marked after heavy opiate premedication (Bryce Smith and O Brien 1956 1957) Most clinical reports mention the occurrence of tachypnoea in lightly anaesthetised patients and this is quickly controlled by the intravenous injection of a small dose of pethidine Brennan Hunter and Johnstone (1957) consider tachypnoea to be more related to the surgical stimulation than to the inhalation of halothane

Cardiovascular effects —There seems to be little doubt that the inhalation of halothane produces hypotension in proportion to the depth of anaesthesia This hypotension is usually accompanied by bradycardia Raventos (1956) attributed the blood pressure fall to ganglionic block and postulated a marked effect of the drug on the mesenteric ganglia, with little weakening of cardiac muscle Johnstone (1956) and Brennan, Hunter and Johnstone (1957) support this view on clinical grounds, because of the marked vasodilatation which occurs On the other hand Burn and his colleagues (1957) found that halothane produced a depression of the dog heart lung preparation which was about 70 per cent of that produced by chloroform and much greater than the effects of comparable concentrations of

ether and trichloroethylene Although they found that halothane can weaken ganglionic transmission (and potentiate hexamethonium) they considered that this was not of such intensity as to account for the hypotension and suggested a central depression of the vasomotor mechanisms as another possible explanation In support of this they found that depression of a central nervous system reflex, the knee jerk, occurred in proportion to the degree of hypotension Hypotension indeed seems to be the most important drawback to the use of halothane in clinical anaesthesia Brindle and his colleagues (1957) report severe postural hypotension from subanaesthetic concentrations of the vapour during occipital craniotomy carried out in the sitting position It rapidly responds to lightening of the depth of anaesthesia and the use if necessary, of the vasopressors methoxamine and phenylephrine As will be mentioned later, infusions of adrenaline or noradrenaline should not be used to restore normal blood pressure

The preservation of vagal activity in the presence of halothane is the cause of the bradycardia (Raventos, 1956) However there seems sometimes to be a relation ship between the blood pressure and pulse rate which is similar to the von Bezold response seen in patients who have received veratrum alkaloids (Dawes Mott and Widdicombe, 1951) Johnstone (1956) recommended that an additional 0 6 milli gram atropine be given with the induction dose of thiopentone and commented on the rise of blood pressure which accompanies a tachycardia Chang McCartney and Graves (1957) have verified the value of an additional dose of atropine to reduce the degree of hypotension It has also been suggested that where an antidepolarising type of relaxant is to be used in conjunction with halothane gallamine triethiodide is the drug to use because of its specific action in depressing the ability of the vagus to slow the heart (Riker and Westcoe 1951)

Serious abnormalities in cardiac rhythm are not commonly seen during halothane anaesthesia although multifocal ventricular extrasystoles have been observed (Johnstone 1956) Ventricular fibrillation sometimes occurred following injection of adrenaline in animals (Raventos 1956) and Brindle Gilbert and Millar (1957) have found this to be a hazard in man In a series of neurosurgical patients they found a higher incidence of serious disturbances in rhythm when adrenaline was used with the local anaesthesia Amounts up to 500 milligrams of adrenaline were injected (in 125 millilitres of 1 1 500 cinchocaine) and a rise in the adrenaline content of peripheral venous blood was detected in these patients up to 15 minutes after its administration Pending further investigation it appears from their evidence that the subcutaneous injection of adrenaline during halothane anaesthesia in man may be hazardous and other vasopressors should therefore be employed to correct hypotension The potential hazard due to endogenous adrenaline must also be remembered Robson and Sheridan (1957) have observed bursts of ven tricular extrasystoles during stretching of the rectal sphincter under light halothane anaesthesia and comment that this is reminiscent of events under chloroform anaesthesia

Muscular relaxation—The consensus of opinion in the clinical reports shows that a fair degree of muscular relaxation can be obtained during halothane anaesthesia in man although Burn and his colleagues (1957) demonstrated that concentrations of vapour as high as 4 per cent did not produce neuromuscular block in animals These workers found that halothane antagonises the action of suxamethonium and potentiates *d* tubocurarine chloride The antagonism of

suxamethonium by halothane does not seem to be of great clinical significance, but severe blood pressure falls have followed the administration of *d* tubocurarine chloride *during halothane anaesthesia*. This is attributed to a potentiation of the ganglion blocking action of the relaxant. Gallamine triethiodide appears to be devoid of this hazard. Following the use of muscle relaxants, Johnstone (1956) stresses that a profound cardio inhibitor, such as neostigmine, is dangerous in patients who have had halothane and its use has caused some anxiety even when it has been preceded by the usual dose of atropine.

Metabolic effects.—In contrast to chloroform and ether anaesthesia, halothane does not produce marked hyperglycaemia (Stephen and his colleagues, 1957), in fact it may induce sensitivity to insulin in diabetic patients (Brennan, Hunter and Johnstone, 1957). Impairment of bromsulphalein excretion has been reported after long anaesthesia in man by Brindle, Gilbert and Millar (1957) but Burns, *Mushin, Organe and Robertson (1957) and Stephen and his colleagues (1957)* consider the effects of halothane on liver function to be no more marked than those of other anaesthetic agents.

Other effects.—Raventos (1956) found dilatation of the proximal convoluted renal tubules with slight cytological changes in the cells of these tubules in animals, after repeated periods of anaesthesia with halothane. Renal function tests, carried out in man by Burns, Mushin, Organe and Robertson (1957) and by Robson and Sheridan (1957) did not reveal any specific toxic effects of the drug on the kidneys.

Opinions differ on the incidence of post operative nausea and vomiting after halothane. Brennan and his colleagues (1957) and Stephen and his colleagues (1957) quote a 6 per cent incidence in over 3,000 administrations, while Burns *and his colleagues (1957) place the incidence at 28 per cent.*

Clinical use.—There is not complete agreement as to the optimum inhaled concentrations of halothane for the production of surgical anaesthesia. Mackay (1957) and Bryce Smith and O'Brien (1957) used 2–3 per cent for induction of anaesthesia. For maintenance, Bryce Smith and O'Brien found that about a 2 per cent vapour was required, while Mackay's figure was 0.5–1 per cent. This discrepancy may be explained by the concomitant use of nitrous oxide and oxygen by Mackay, whereas Bryce Smith and O'Brien volatilized the *drug with air*. The importance of vaporizers capable of delivering low concentrations of the drug must be stressed. With a circle absorber Gain and Paletz (1957) have rapidly reached E.E.G. level 7, with accompanying cardiovascular and respiratory depression, whereas Stephen and his colleagues (1957) have *found that level 3* appeared to produce satisfactory anaesthesia. All cases of cardiac arrest reported during halothane anaesthesia have undoubtedly been due to inadvertent overdosage (Chang, Macartney and Graves, 1957, Foster, 1957, Hudon, Jacques, Clavet and Houde, 1957).

It is too early even to suggest whether halothane will prove to have a useful place *in clinical anaesthesia*. Its great advantages are lack of inflammability and stability in contact with soda lime. However, it has disadvantages compared with trichloroethylene as far as hypotension, respiratory depression and lack of analgesic properties are concerned. The concentration of vapour required for anaesthesia is low and once vaporizers are available which will allow considerable variation within this range, it is hoped that many of these dangers may be minimized. The possible sensitization of the myocardium to adrenaline by

halothane must also be remembered, particularly since the report of several instances of primary cardiac failure during the administration of trichloroethylene, due undoubtedly to this property, which formerly was considered to be a purely theoretical disadvantage of this agent (Edwards and his colleagues, 1956)

There is a need for a non inflammable flexible volatile agent, capable of administration by simple means, yet which can be used safely in the closed circuit However, these advantages must not be obtained at the price of safety in other aspects of its clinical use

INTRAVENOUS ANAESTHESIA

Thiobarbiturates

Apart from a limited use of thiamylal in the United States of America and thialbarbitone in Britain and elsewhere, for the past twenty years thiopentone has remained the most commonly used thiobarbiturate Advantages over thiopentone have been claimed for both thiamylal and thialbarbitone, and these can be demonstrated by a close study of their actions However, if one allows for differences in potency, there is little to choose between the three barbiturates so far as their clinical use is concerned This is shown by the failure to distinguish between thiopentone and thiamylal in a double blind clinical study involving over one thousand administrations of each drug (Tovell and his colleagues, 1955)

Thiopentone is a well tried and reliable drug, and, if its actions and limitations are fully appreciated, it can be given safely to the majority of patients This was shown by its use between 1934 and 1955 in over one third of three and a half million anaesthetics recently reviewed by the author (Dundee, 1956) From the patients viewpoint, its widespread use has been a great advance and has removed much of the terror of operation To displace such a drug a new compound must have clear cut advantages and should be assessed in the light of the hazards inherent in thiopentone

Studies of mortality associated with anaesthesia show that the depressant action of thiopentone on the circulation is a too frequent cause of death The sequelae of inadvertent intra arterial injection are too well known to need stressing Respiratory depression leading to hypoxia is another danger associated with the use of thio pentone Delayed recovery is not a major drawback and is rarely found after the judicious use of the drug but the return of consciousness does not mean that the patient has complete control of the mental faculties Failure to appreciate this has led to accidents Although the period of narcosis is usually brief after small amounts of thiopentone, recovery may be prolonged after large doses, especially when the drug is used as sole narcotic The lack of analgesic properties makes this last use unsafe as doses which suppress reflex activity invariably have an adverse effect on other vital functions

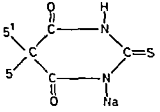
In the field of thiobarbiturates many drugs with variations in the side chains as compared with thiopentone have been tried in anaesthesia In these the aim seems to be the production of a shorter acting compound by more rapid degradation or redistribution in the body N methyl thiobarbiturates are definitely shorter acting in small doses and less cumulative after repeated injection (Swanson and Chen, 1953, Stoelting 1953 Stoelting and Graf 1954) Papper and his co workers (1955) have shown that the shorter duration of narcosis with n methyl thiopentone

as compared with thiopentone is due to its greater affinity for body fat However since this advantage of brevity of action was accompanied by an increased incidence of laryngospasm and hiccough, these drugs have no clinical importance

The structural formulae for three other new thiobarbiturates are given in Table II Buthalitone is about half as potent as thiopentone whereas methothiourate and Inactin seem to be about two thirds as strong *Buthalitone and methothiourate* have now been subjected to extensive clinical trials, and on reviewing these critically (*see* bibliography) there is some not very definite evidence of more rapid recovery following small doses Blake and Perlman (1956) have shown that methothiourate accumulates in fat more rapidly than thiopentone It is not yet definitely known whether prolonged narcosis follows large doses of these drugs, as is the case with thiopentone Fitzpatrick, D Arcy and Mersch (1956) claim that this does not happen with methothiourate, whereas Bourne (1956) thinks that with equipotent doses narcosis from buthalitone lasts rather longer than from thiopentone

TABLE II

STRUCTURAL FORMULAS FOR THIOPENTONE, BUTHALITONE, METHOTHIOURATE AND INACTIN



	5	5'
Thiopentone Thiopental	CH_3-CH_2-	$CH_3-CH_2-CH_2-CH(CH_3)-$
Buthalitone (Baytinal) (Transithal) (Ulbreval)	$CH_2-CH=CH_2-$	$(CH_3)_2CH-CH_2-$
Methothiourate (Methitural) (Neraval) (Thiogenal)	$CH_3-CH_2-CH_2-CH(CH_3)-$	$CH_3-S-CH_2-CH_2-$
Inactin	CH_3-CH_2-	$CH_3-CH_2(CH_3)CH-$

On the debit side Nobes (1955) and Little and Reid (1956) with buthalitone and Fitzpatrick, D Arcy and Mersch (1956) and Boone, Munoz and Dillon (1956) with methothiourate, report a higher incidence of respiratory disturbances than one usually associates with thiopentone This may be due to lack of experience with the drugs, but in light of the findings with n methyl thiobarbiturates, one wonders whether such occurrences are not inevitable with small doses of extremely short acting thiobarbiturates If the narcosis returns rapidly to a level where coughing is likely before an effective supplementary agent can be introduced, one may have to use an amount for an induction dose which has as long an action as thiopentone With intermittent *injection more frequent increments will* be required and any possible advantages from the use of small doses will be lost Fitzpatrick, D Arcy and Mersch (1956) claim that the continuous use of a dilute solution of metho thiourate abolishes the risk of laryngospasm, coughing and hiccough, and this

supports the hypothesis that such effects are due to too rapid lightening of anaesthesia.

For electroconvulsive therapy and minor or dental surgery, especially in out patients, one welcomes a drug from which recovery will be more rapid than from thiopentone. From the published reports it would seem that we have at least two such drugs, the relative merits of which have yet to be established. It also seems unlikely that the same drugs can replace thiopentone, thialbarbitone or thiamylal as a routine induction agent for major surgery or where intermittent administration is intended. None of these new drugs appears to be less toxic to the cardiovascular system. Respiratory depression may be of shorter duration, by virtue of a more rapid recovery from anaesthesia. Methothiourate is not free from irritant effects after extravenous injection (Grant Whyte, 1956).

From the above discussion on buthalitone and methothiourate it appears that we are no nearer finding a completely trouble free intravenous thiobarbiturate. Inactin is as yet uninvestigated in the English speaking world but Continental reports show it to be very similar to thiopentone.

Only two suggestions have been made recently which appear to have any bearing on the problem of reducing the inherent toxicity of the thiobarbiturates. Gould (1955), Hasler (1955) and Dawkins (1955) all claim that hexobarbitone is less irritant to tissues than is thiopentone and suggest its more widespread use in anaesthesia. The beneficial effects of calcium chloride in preventing myocardial depression caused by thiopentone has been described by Fronek and Pisa (1956). It remains to be seen whether these suggestions are of any clinical value. Mean while attempts are being made to seek intravenous anaesthetic agents which are not barbiturates. These will have to be judged using thiopentone as a yardstick.

Steroids

Selye (1941, 1942) investigating different steroids observed general anaesthesia after their use in animals. Laubach, P An and Rudel (1955) and P An and his colleagues (1955) extended this work and selected 21 hydroxypregnane 3, 20 dione sodium hemisuccinate as most likely to be of clinical use. This drug now known as hydroxydione (Viadril) possesses a high margin of safety in animals and appears to be devoid of oestrogenic or androgenic stimulating properties. After intravenous injection there is a delay of a few minutes before the onset of narcosis. Experiments by Taylor and Shearer (1956) suggest that the drug has hypnotic rather than analgesic properties. Hypotension and respiratory depression accompany narcosis but hydroxydione does not depress the isolated rabbit heart to the same extent as does thiopentone although the duration of its effect is longer. It has been suggested that inhibition of the central vasoconstrictor centres is the main factor in the production of hypotension.

Hydroxydione is a water soluble white crystalline substance aqueous solutions having a pH of 8 to 10. All clinical reports refer to its irritant effect on the endothelium of the veins. Using a 2.5 per cent solution injected into a rapidly running infusion, Murphy, Guadagni and Debon (1955) found a 3 per cent incidence of venous thrombosis; with a similar technique Lerman (1956) found two cases of thrombophlebitis in 19 administrations. With an 0.5 per cent and 1.5 per cent solution Taylor and Shearer (1956) found 20 per cent incidence of thrombosis and in 139 cases reported by Dent, Wilson and Stephen (1956) with a 1 per cent

solution 23 9 per cent of patients complained of a burning aching pain near the site of injection and a 77 5 per cent incidence of thrombophlebitis occurred

The most striking difference between the action of hydroxydione and that of the thiobarbiturates is the delayed onset of sleep This is affected by the dose, rate of injection and condition of the patient, and varies between two and five minutes

During the period between injection and loss of consciousness the patients appear to be free from fear and apprehension, and gradually become more sleepy until they can no longer talk There is another delay between loss of consciousness and the maximum effect being observed It seems advisable to allow 5-10 minutes after injection before attempting intubation or bringing the patient into the theatre Half a gramme renders the average adult drowsy but usually not unconscious whereas one gramme usually produces deep sleep

Intubation can easily be performed without relaxants in the majority of cases after hydroxydione but the reflexes remain active and coughing is common The jaw relaxes early and respiratory obstruction is liable to occur, but an oropharyngeal airway is well tolerated Persistent hiccough has been reported by Harbord and Wild (1956) in 9 of 25 cases but this complication is not stressed by other workers Respiratory depression is not marked after moderate doses of hydroxydione Abnormal muscle movements have been observed in isolated cases and may occur spontaneously or result from stimulation

Tachycardia of varying degree was a usual finding during anaesthesia and hypotension seemed to be related to the dose of hydroxydione used Hunter (1957) has noted that the main immediate complications of fall in blood pressure and respiratory depression do not appear until some time after the administration of the drug has been stopped The variety of techniques used for the maintenance of anaesthesia makes it difficult to assess the other effects of this new anaesthetic agent Muscular relaxation appears to be variable After one gramme of hydroxy dione one can expect an average adult to be awake and rational but still drowsy at the end of one and a half hours Galley and Rooms (1956) comment on the feeling of well being during the recovery period

Hydroxydione is an interesting drug and yet it would seem to possess all the disadvantages that are possible in an intravenous anaesthetic agent The onset of narcosis is delayed and minute to minute control of the depth of anaesthesia is impossible Delay in recovery is common and venous thrombosis must be con sidered a major disadvantage However, it opens up a new field with a type of anaesthetic agent which has not hitherto been explored Before passing judgment on it one should wonder what would have happened if the early members of the barbiturate group of drugs for example barbitone had been subjected to an extensive trial as intravenous anaesthetics It is hoped that other steroids will be investigated and among these one may yet find a drug superior to thiopentone

Dolitrone

This drug is different from any other agent used in intravenous anaesthesia Its pharmacology was described by Thompson, Smith and Werner in 1954 and the first clinical trials were reported by Lundy (1954 1955 1956) These reports suggested that Dolitrone was primarily an analgesic, although anaesthesia could be produced with large doses It was suggested by Lundy that Dolitrone might open up an era of general analgesia , and he described the satisfactory use of

supports the hypothesis that such effects are due to too rapid lightening of anaesthesia

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Only two suggestions have been made recently which appear to have any bearing on the problem of reducing the inherent toxicity of the thiobarbiturates Gould (1955) Hasler (1955) and Dawkins (1955) all claim that hexobarbitone is less irritant to tissues than is thiopentone and suggest its more widespread use in anaesthesia The beneficial effects of calcium chloride in preventing myocardial depression caused by thiopentone has been described by Fronek and Pisa (1956) It remains to be seen whether these suggestions are of any clinical value Mean while attempts are being made to seek intravenous anaesthetic agents which are not barbiturates These will have to be judged using thiopentone as a yardstick

Steroids

Selye (1941 1942) investigating different steroids observed general anaesthesia after their use in animals Laubach, P An and Rudel (1955) and P An and his colleagues (1955) extended this work and selected 21 hydroxypregnane 3, 20 dione sodium hemisuccinate as most likely to be of clinical use This drug now known as hydroxydione (Viadril) possesses a high margin of safety in animals and appears to be devoid of oestrogenic or androgenic stimulating properties After intravenous injection there is a delay of a few minutes before the onset of narcosis Experiments by Taylor and Shearer (1956) suggest that the drug has hypnotic rather than analgesic properties Hypotension and respiratory depression accompany narcosis but hydroxydione does not depress the isolated rabbit heart to the same extent as does thiopentone although the duration of its effect is longer. It has been suggested that inhibition of the central vasoconstrictor centres is the main factor in the production of hypotension

Hydroxydione is a water soluble white crystalline substance aqueous solutions having a pH of 8 to 10 All clinical reports refer to its irritant effect on the endo thelium of the veins Using a 2 5 per cent solution injected into a rapidly running infusion, Murphy Guadagni and Debon (1955) found a 3 per cent incidence of venous thrombosis with a similar technique Lerman (1956) found two cases of thrombophlebitis in 19 administrations With an 0 5 per cent and 1 5 per cent solution Taylor and Shearer (1956) found 20 per cent incidence of thrombosis and in 139 cases reported by Dent, Wilson and Stephen (1956) with a 1 per cent

is prolonged and recovery is seldom prompt Respiratory depression is minimal but tachycardia and hypotension result from large doses One advantage stressed by Harrison is the pain free post operative period after the use of the pheno thiazine analgesic mixture The most commonly used mixture consists of 50 milligrams of chlorpromazine and 100 milligrams of pethidine diluted in saline solution to 20 millilitres or added to a dextrose or saline infusion The use of 12 5 milligrams of chlorpromazine and 25 milligrams each of promethazine and pethidine administered intravenously following a minimal dose of thiopentone to provide basal narcosis during epidural anaesthesia is being exploited successfully by Evans (1956)

It is not proposed to discuss the theory of block of the autonomic nervous system which is the basis of the use of phenothiazine derivatives in shocked patients but their beneficial use in conjunction with fluid replacement, has been described by Kenny (1956) As mentioned above it is surprising that no definite conclusions have been reported on the value of the phenothiazines as agents for the production of anaesthesia They cannot, as yet, be considered in any way to compete with the thiobarbiturates for routine anaesthesia

NITROUS OXIDE

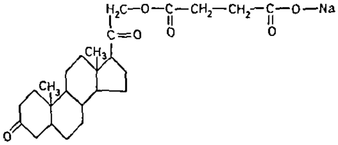
It may seem strange to include the first gaseous anaesthetic agent in a book on modern trends in anaesthesia For many years nitrous oxide anaesthesia was associated with varying degrees of hypoxia, especially in the secondary saturation technique described by McKesson (1926) The sequelae of hypoxia have been described fully by Courville (1939), Fletcher (1945) and others In the absence of hypoxia, nitrous oxide was considered a weak anaesthetic gas and its main use in prolonged operations was as a vehicle for volatile agents Recently, this view has changed drastically in keeping with the present concept of lighter planes of anaesthesia and this section draws attention to these new concepts of the use of nitrous oxide

From experiments in healthy unpremedicated volunteers Gray (1954) established that loss of consciousness occurs without hypoxia with an arterial blood con centration of 20 volumes of nitrous oxide per 100 millilitres of blood With closed circuit anaesthesia this is not achieved until after 40–50 minutes with gas flows of one litre nitrous oxide and one litre oxygen per minute Increasing the nitrous oxide flow to two litres per minute decreased this time to ten minutes From these studies it is obvious that with large gas flows the more rapid elimination of nitrogen from the alveoli will hasten the onset of anaesthesia, and also that non hypoxic mixtures of nitrous oxide and oxygen can produce unconsciousness Hamilton and Eastwood (1955) with Miles, Martin and Adriani (1956) studying the elimination of nitrogen found that with flow rates equal to the minute respiratory volume of the subject denitrogenation takes place in two to three minutes The absence of rebreathing is essential for this rapid elimination and with spontaneous respiration there is no advantage in the use of excessively high gas flows

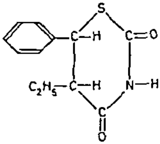
Severinghaus (1954) has shown that nitrous oxide continues to be taken up in solution in the body for many hours, so the concentration in the reservoir bag will fall when the flow of nitrous oxide is stopped, even after several hours provided the oxygen flow is at least sufficient to meet metabolic needs At the end

subhypnotic doses for such painful procedures as burn dressings, haemorrhoidectomy and dental extractions The lack of depressant effects on the cardiovascular and respiratory systems was stressed as well as its depressant action on the pharyngeal and largyngeal reflexes

Subsequent studies by Tait and his colleagues (1956) have not confirmed Lundy's favourable impressions of Dolitrone They concluded that it was devoid of analgesic action It provided a rapid and pleasant induction, but recovery was not so prompt as after a sleep dose of thiopentone If used in large doses as a sole agent, both hypotension and respiratory depression occurred The incidence of laryngospasm (15 9 per cent) and recurrent coughing (39 1 per cent) was much greater than one would expect with thiopentone Other workers have found a dose of 30 milligrams per kilogram Dolitrone to be equipotent with 20 milligrams per kilogram of thiopentone in the dog and the cardiovascular effects of these doses of each drug were approximately the same (Cotten and Bay 1956)



Hydroxydione (Viadril) (21 hydroxypregnane 3 20 dione sodium hemisuccinate)



Dolitrone (5-ethyl 6-phenyl m thiazine 2 4-dione)

The same comments can be made on Dolitrone as on hydroxydione It would appear to be a less satisfactory agent than the drugs already available However, it also indicates a new type of drug for study and with modifications of the molecule an agent superior to thiopentone may emerge

Phenothiazine derivatives

The use of these drugs (especially promethazine chlorpromazine and diethazine) in combination with pethidine as sole agents in anaesthesia was first introduced by Continental workers and de cribed by the term artificial hibernation The principles of their use are outlined fully in the publication of Laborit and Huguenard (1954) The enthusiasm shown by these authors has not spread outside Europe with the rapidity which one might have expected from the results which they have claimed This may have been due to the rather vague and tenuous arguments on which the technique was based and the absence of clear cut controlled clinical data to support them Nevertheless some of the phenothiazine derivatives especially chlorpromazine appear to have a definite place in selected cases (Baxter Bolster and McKechnie 1954 Ashworth 1956 Albert and his co workers 1956 Sadove 1956)

Reports by Smith and Fairer (1953) and Harrison (1955) show certain similarities between the phenothiazine analgesic combination and steroid anaesthesia Administration is carried out over a period of 5–10 minutes the onset of narcosis

changes were not of the very slow single pattern characteristic of ether and cyclo propane and level three was not exceeded Xenon oxygen appeared to be free from toxic effects on the cardiovascular system The blood pressure remained constant with a tendency to tachycardia No serious electrocardiographic changes were reported Respiratory depression was not noted but oxygenation remained satisfactory throughout Recovery from anaesthesia was invariably prompt Animal experiments demonstrated an absence of toxic effects on brain lung liver, kidneys and adrenals after 48 hours of xenon oxygen anaesthesia (Bracken, Burns and Newland 1956)

By administration of xenon oxygen at elevated pressures in monkeys, Pittinger and his colleagues (1955) were able to obtain profound anaesthesia and apnoea occurred early in the administration The increasing depth of anaesthesia was not associated with hypoxaemia Appreciable rhythmic electroencephalographic activity persisted during profound xenon anaesthesia, and the apparent clinical depth of anaesthesia with this agent exceeds the electroencephalographic evidence of cortical depression based on scales derived from ether or cyclopropane anaesthesia In view of the observation of Pittinger and his colleagues (1954) that there is a more rapid uptake of xenon by subcortical structures than by cortical tissue the electroencephalographic changes may indicate that cortical mechanisms are relatively less affected by xenon than by ether or cyclopropane

It is of theoretical interest that a chemically inert gas can produce a pharmaco logical effect It has the advantage of being non explosive However, the anaesthetic properties of xenon are not so much superior to those of nitrous oxide as to justify its higher cost for routine use

CONCLUSION

The modern trend in general anaesthesia seems to be the adoption of a lighter level of narcosis and the increasing use of analgesics We may well be moving towards an era of general analgesia rather than general anaesthesia This is shown by work described above in relation to nitrous oxide and ether analgesia and more recently by Hayward Butt and his colleagues (1957) who have termed it ataralgesia

REFERENCES

Adriani J (1952) *Pharmacology of Anaesthetic Agents* 3rd ed Springfield Thomas

Albert S N Spencer W A Finkelstein M and Coakley C S (1956) *Curr Res Anesth* 35 101

Artusio J F (1954) *J Pharmacol* 111 343

— (1955) *J Amer med Ass* 157 33

Ashworth H K (1956) *Med Pr* 236 399

Baxter R W Bolster J A and McKechnie S (1954) *Anaesthesia* 9 79

Bellville J W and Artusio J F (1955) *Anesthesiology* 16 379

Blake M W and Perlman P L (1956) *J Pharmacol* 117 287

Boone J D Munoz R and Dillon J B (1956) *Anesthesiology* 17 284

Bourne W (1956) *Proc R Soc Med* 49 736

— McDowell J F and Whyte J C (1937) *Curr Res Anesth* 16 46

Bracken A Burns T H S and Newland D S (1956) *Anaesthesia* 11 40

Brennan H J Hunter A R and Johnstone M (1957) *Lancet* 2 453

Brindle C F Gilbert R B G and Millar R A (1957) *Canad Anaesth Soc J* 4 265

of anaesthesia the high concentration of nitrous oxide in the tissues is rapidly reduced but complete removal is slow Arterial blood loses 70 per cent of its nitrous oxide in 3 minutes and 90 per cent in 20 minutes The elimination of this large volume of nitrous oxide at the end of anaesthesia results in a lowered alveolar oxygen tension (Fink, 1954) and may be enough to produce arterial oxygen unsaturation in the presence of adequate ventilation if the patient is allowed to breathe room air

An appreciation of the analgesic properties of non hypoxic mixtures of nitrous oxide and oxygen is another essential of this new concept of the place of this gas in anaesthesia Klock (1951, 1955) has described a plane at the lower border of the first stage of anaesthesia, which he calls amnalgesia This is similar to the plane of total analgesia with ether described by Artusio (1954) and it permits a wide range of operations not requiring muscular relaxation, to be performed without pain or memory The electroencephalographic pattern of this level of anaesthesia has been described by Wasmuth and Hale (1954)

There are many clinical reports of the use of the non hypoxic mixtures of nitrous oxide and oxygen in anaesthesia Foldes Ceravolo and Carpenter (1952) have used this with or without relaxants after a preliminary dose of thiopentone in over 10 000 patients Rubin (1953) considers that by avoiding the use of central depressants, there are no absolute contraindications to this form of anaesthesia Pre oxygenation, which ensures removal of practically all the nitrogen from the alveoli and therefore hastens induction with a mixture containing 70 to 80 per cent nitrous oxygen has been used by Gray and Riding (1957) for mitral valvotomy The possibility of excitement or struggling is avoided by the early use of a paralysing dose of *d* tubocurarine chloride A similar technique has been described by Heller Watson and Storrs (1956) for poor risk patients

Klock (1955) has popularized the non hypoxic nitrous oxide and oxygen technique in dentistry and in more than 7,000 cases he has not observed a sudden or alarming fall in blood pressure Tom (1956) advocates the preliminary use of not more than six breaths of pure nitrous oxide He stresses that induction must not be hurried and that mouth breathing must be immediately corrected There is no stertor jactitations or tetany which are so characteristic of the conventional use of dental gas The explosion hazard is completely eliminated and this new concept of nitrous oxide and oxygen anaesthesia whether applied to major or minor surgery deserves serious consideration is one of the greatest advances of the first decade after the centenary of the demonstration of the anaesthetic properties of the gas

INERT GASES

Xenon

In 1951 Cullen and Gross produced surgical anaesthesia in two patients using a mixture of 80 per cent xenon and 20 per cent oxygen After washing out alveolar nitrogen from the patient with oxygen the anaesthetic mixture was administered using a to and fro absorption system Subsequent reports by Pittinger and his colleagues (1953) on five patients and by Morris Knott and Pittinger (1955) on seven cases have shown that the potency of this mixture is similar to that of ethylene and somewhat greater than nitrous oxide The electroencephalographic

Liang, H S and Dodd R B (1956) *Anesthesiology* 17 217
Little A L M and Reid A A (1956) *Lancet* 1 1016
Lockett J (1951) *Brit J Anaesth* 23 117
Lundy J S (1954) *J Amer Nurse Anesthetists* 22 225
— (1955) *J Amer med Ass* 157 1399
— (1956) *Ibid* 162 97
Lu G King J S L and Krantz J C Jr (1953) *Anesthesiology* 14 466
Macdonald T J C (1950) *Brit J Anaesth* 22 99
Mackay I M (1957) *Canad Anaesth Soc J* 4 235
McKesson E I (1936) *Brit med J* 2 1115
Miles G G Martin N T and Adriani J (1956) *Anesthesiology* 17 213
Morris L E Knott J R and Pittinger C B (1955) *Anesthesiology* 16 312
Murphy J J Guadagni N P and Dobson I (1955) *J Amer med Ass* 158 1412
Nobes P A (1955) *Lancet* 1 797
Orth O S (1955) *Fed Proc* 14 376
P'An S Y Gardocki J F Hutcheon D E Rudel H Kodet M J and Laubach G D (1955) *J Pharmacol* 115 432
Papper E M Peterson R C Burns J J Bernstein E Lief P and Brodie B B (1955) *Anesthesiology* 16 544
Pittinger C B Moyers J Cullen S C Featherstone R M and Gross E G (1953) *Anesthesiology* 14 10
— Featherstone R M Gross E G Stickley E E and Levy L (1954) *J Pharmacol* 110 458
— Faulconer A Knott J R Pender J W Morris L E and Bickford R G (1955) *Anesthesiology* 16 551
Raventos J (1956) *Brit J Pharmacol* 11 394
Riker W F Jr and Wescoe W C (1951) *Ann N Y Acad Sci* 54 373
Robson J C and Sheridan C A (1957) *Curr Res Anesth* 36 63
Roualle H L M (1950) *Brit med J* 2 712
Rubin H (1953) *Brit J Anaesth* 25 237
Sadove M S (1956) *J Amer med Ass* 62 712
— Balagot R C and Linde H W (1956) *Anesthesiology* 17 591
— Wyant G M and Cletcher J D (1955) *Curr Res Anesth* 34 235
— Kowalski L F Balagot R C and Krol Z J (1955) *J Amer dent Ass* 51 536
Selye H (1941) *Proc Soc exp Biol* (N Y) 46 116
— (1942) *Curr Res Anaesth* 21 41
— (1942) *Endocrinology* 30 437
— P'An S Y Gardocki J F Hutcheon D E Rudel H Kodet M J and Lawbach G D (1955) *J Pharmacol* 115 432
Severinghaus J W (1954) *J clin Invest* 9 1183
Smith A J and Farrer J G (1953) *Brit med J* 2 2147
Stephen C R Grosskreutz D C Lawrence J H A Fabian L W Bourgeois Gavardin M (1957) *Canad Anaesth Soc J* 4 246
Stoelting V K (1953) *Curr Res Anesth* 32 370
— and Graf J P (1954) *Anesthesiology* 15 61
Swanson E E and Chen K K (1953) *Proc Soc exp Biol* (N Y) 82 212
Tait C A Davis D A Grosskreutz D C and Boniface K J (1956) *Anesthesiology* 17 536
Taylor N and Shearer W M (1956) *Brit J Anaesth* 28 67
Thompson C R Smith J K and Werner H W (1954) *Fed Proc* 13 411
Tom A (1956) *Brit med J* 1 1085
Tovell R M Anderson C C Sadove M S Artusio J F Papper E M Coakley C S Hudon F Smith S M and Thomas G J (1955) *Anesthesiology* 16 910
Wasmuth C E and Hale D E (1954) *Cleveland Clin Quart* 21 1

ADDITIONAL BIBLIOGRAPHY

Buthalitone sodium

Davidson J and Love W (1956) *Brit J Anaesth* 28 377

Bryce-Smith R and O Brien H D (1956) *Brit med J* 2 969
— and — (1957) *Proc R Soc Med* 50 193
Burn J H Epstein H G Feigan C A and Paton W D M (1957) *Brit med J* 2 479
Burns T H S Mushin W Organe G S W and Robertson J (1957) *Brit med J* 2 483
Chang J Macartney H H and Graves H B (1957) *Canad Anaesth Soc J* 4 187
Cope D H P (1950) *Brit med J* 2 1116
— McDowell J F and Whyte J C (1937) *Curr Res Anesth* 16 46
Courtin R F Bickford R G and Faulconer Jr (1950) *Proc Mayo Clin* 27 197
Courville C B (1939) *Untoward Effects of N O Anaesthesia* California Pacific Press
Cotten M de V and Bay E (1956) *Anesthesiology* 17 103
Cullen, S C and Gross E G (1951) *Science* 113 580
Dawes G S Mott J C and Widdicombe J G (1951) *Brit J Pharmacol* 6 675
Dawkins, C J M (1955) *Anaesthesia* 10 198
Dent S J Wilson W P and Stephen, G R (1956) *Anesthesiology* 17 672
Di Giovanni J and Dripps, R D (1956) *Anesthesiology* 17 353
Dornette W H L and Orth O S (1955) *Curr Res Anesth* 43 26
— Brasman R D and Orth O S (1954) *Fed Proc* 13 349
Dundee J W (1956) *Thiopentone and Other Thiobarbiturates* Edinburgh Livingstone
— and Dripps, R D (1957) *Anesthesiology* 18 282.
— Linde H W and Dripps R D (1957) *Anesthesiology* 18 66
Edwards, G Morton H J V Pask E A and Wylie W D (1956) *Anaesthesia* 11 194
Elam J E and Moorhouse M L (1951) *Brit med J* 1 13
Evans F T (1956) Anaesthesia for the Aged *Modern Trends in Geriatrics* London Butterworths
Fink B R (1954) *Acta anaesth belg* 5 42
Fitzpatrick L J D Arcy C C and Mersch M M (1956) *Anesthesiology* 17 684
Fletcher D E (1945) *J nerv ment Dis* 102, 4
Foldes, F F Ceravolo A J and Carpenter S L (1952) *Ann Surg* 136 978
Foster C A (1957) *Lancet* 1 1144
Fronek A and Pisa, Z. (1956) *Brit J Anaesth* 28 366
Gain E A and Paletz, S G (1957) *Canad Anaesth Soc J* 4 289
Gainza, E Heaton C E. Willcox, M and Virtue R W (1956) *Brit J Anaesth* 28 411
Galley A H and Rooms, M (1956) *Lancet* 1 990
Goldschmidt, S Ravdin, I S Lucke B Muller G P Johnston C G and Ruig, W L (1934) *J Amer med Ass* 102, 21
Gould R B (1955) *Anaesthesia* 10 91
Grant Whyte H (1956) *S Afr med J* 30 905
Gray T C (1954) *Ann R Coll Surg Engl* 15 402.
— and Riding J E (1957) *Anaesthesia* 12, 129
Hamilton W K and Eastwood, D W (1955) *Anesthesiology* 16 861
Harbord, R P and Wild, W N (1956) *Proc R Soc Med* 49 487
Harrison G (1955) *Brit J Anaesth* 27 131
Hasler J K (1955) *Anaesthesia* 10 91
Hayward Butt J T (1957) *Lancet* 2, 972
Heller M L Watson T R and Storrs, R C (1956) *J Amer med Ass* 161 1534
Hudon, F Jacques, A Clavet M and Houde J (1957) *Canad Anaesth Soc J* 4 221
Hunter A R (19 7) *Anaesthesia* 12, 10
Johnstone M (1956) *Brit J Anaesth* 28 392
Kenny S (19 6) *Brit med J* 2, 211
Klock, J H (1951) *Curr Res Anesth* 30 151
— (1955) *Curr Res Anesth* 34 379
Krantz, J C Evans, W E Carr C J and Kibler D V (1946) *J Pharmacol* 86 138
— Carr C J Musser R D and Sauerwald J J (1947) *J Pharmacol* 89 88
— — Lu, G and Bell F K (1953) *J Pharmacol* 108 488
Laborit, H and Huguenard, P (1954) *L Hibernothérapie en médecin et chirurgie* Paris Masson
Laubach, G D P An S Y and Rudel H W (1955) *Science* 122 78
Leake C D and Chen, M Y (19 0) *Proc Soc exp Biol (N Y)* 28 151
Lerman L H (1956) *Brit med J* 2, 129

CHAPTER 3

NEW CONCEPTIONS OF CONSCIOUSNESS

W GREY WALTER

PHYSIOLOGISTS are reluctant to use the term consciousness because the classical methods of physiological investigation require the isolation of a single variable and consciousness must at least involve the coordinated activity of many systems This point has been made most tersely by saying that physiologists only study scious ness that is, the response of a single element such as a nerve cell, to an afferent signal There is at the present time no established technique for recording and comparing the activities of many individual nerve elements at the same time—when this can be accomplished our understanding about central nervous action will at once become more profound and more fertile There is, therefore, a wide gap between academic physiological researches dealing with basic nervous action and those developed for the clinical investigation of human beings A reasonable analogy with the evolution of clinical neurophysiology is the intellectual transition between the mechanics of solid bodies and the behaviour of gases The Newtonian principles underlying the gravitation and motion of two bodies are easily applied and completely rigorous The introduction of a third body enormously complicates the situation and beyond this scale the system becomes a statistical population for which another set of laws apply—the gas laws Direct extrapolation from the two body or three body problem to the kinetic theory of gases is neither easy nor altogether legitimate nor are we justified in seeking a complete description of brain function in the axioms and rules of classical neurophysiology For the time being then we must be content to treat the human brain as if it were a sort of nerve gas consisting indeed of innumerable neuro molecules, but in so vast a number that the character and fate of an individual element is negligible and obscure At the same time we must not forget the ineluctable fact that there are many types of nerve cell and elaborate systems of interconnection between them

If we now attempt to apply these general notions to the conception of consciousness we find that we must accept at the outset the general proposition that any estimate of conscious behaviour must be based on statistical or probabilistic measures of both environment and organism

THE RELEVANCE OF LOGICAL REASONING TO THE PROBLEM OF CONSCIOUSNESS

As an essay in the application of this notion we may start with the assertion that logical reasoning—which is often considered synonymous with thinking—is not relevant to the problem of consciousness This assertion has an important implication it introduces the issue of whether a mechanical man made contrivance can

Dietmann K (1954) *Der Chir* **25** 185
Freuchen P (1956) *Ugeskr Laeg* **118** 1065
Weese H and Koss F H (1954) *Dtsch med Wschr* **79** 601
Williams J E (1956) *Med J Aust* **2** 441
Young D S (1956) *Proc R Soc Med* **49** 735

Inactin

Becher H (1953) *Med Mschr* **3** 655
— (1954) *Med Mschr* **4** 252
Hellman R (1953) *Zbl Gynak* **7** 255
Koster K von (1954) *Der Tuberkulosearzt* **8** 4
Kronschwitz H (1954) *Zbl Chir* **79** 1966
Magistris V F (1954) *Wien med Wschr* **104** 902
Richter W H (1954) *Zbl Chir* **79** 277

Methothiourate

Baltzer H and Salewsky R (1954) *Zbl Gynak* **76** 1723
Benolken A (1955) *Der Landarzt* **31** 65
Luttichan E (1955) *Der Anaesthesist* **4** 9
Mellin P (1955) *Der Anaesthesist* **4** 8
Melon R and Berthier J (1956) *Anesth Analg Paris* **13** 745
Mussgnung G (1955) *Ärztliche Wschr* **10** 89
Scherer G (1954) *Med in Klin* **49** 923

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be described as conscious in a useful sense This may sound trivial and far removed from the basic problems of anaesthesia, but it should be remembered that the theory and practice of automata have advanced to an astonishing degree during the last decade or so, and that recent ideas about brain physiology have been more clearly embodied in models than in verbal or mathematical expressions

Cybernetic hypothesis

The introduction of arguments about machines in a discussion of living creatures (or *vice versa*) is sometimes nowadays referred to as a cybernetic approach The basic hypothesis of cybernetics is that there are general laws governing control and communication which apply equally to animals, machines and societies Cybernetics includes strategies for studying and controlling complex systems whose behaviour would be perturbed by isolation of the various interacting elements The cybernetic approach is therefore valuable for studying living creatures and complex machines in which the behaviour of the whole is hard to predict from the functions of the parts especially when isolation or dissection of the parts may result in irreversible change or irreparable damage Generally, a cybernetic method involves (a) experimental arrangements for the simultaneous observation or control of several variables and (b) the testing of hypotheses derived from such observations by their embodiment in analogue computers or working models A valuable by product of cybernetics is of course the design of automatic machinery to extend or replace human faculties Among these automatic machines are many that are specially designed for the solution of logical problems by human standards they are capable of logical reasoning of a very high order They can also make discriminating judgements and can operate to ensure their own survival and repair, but these capacities do not imply that their behaviour is necessarily conscious in the sense that the writer and reader of these lines are conscious For the most part automatic reasoning machines may be described as having a high degree of sciousness

This is not to say that no machine whatever can be considered conscious—we are limited by our original assertion to the definition of logical reasoning instruments and these form only one of the many possible classes of automata The important conclusion is that a system for logical reasoning does not need more than sciousness and therefore no feature such as consciousness is included in their performance specification

In case there should be any misconception about the working material of cybernetics we should recall that this way of thinking about complex systems is in no way dependent on electronic or algebraic conventions In so far as a cybernetic approach to a biological problem involves the use of analogy or simulation—and this is only a part of the discipline—the material or construction of the analogue is irrelevant Indeed the best analogue may be a paper model hydraulic mechanical and chemical systems have been invoked with great power The accessibility plasticity and high speed of electronic devices make them particularly convenient for cybernetic purposes but they have no unique claim to this field As a corollary to this the inclination to imagine nervous events as essentially electrical should be carefully controlled we know that in fact every signal in the nervous system is an intricate combination of chemical and electrical processes and the mutual interaction between these forces is itself a fertile domain for cybernetic cultivation

The "logical" spinal reflex

We have suggested that the performance of logical tasks by simple artificial machines disposes of the connection between logical reason and consciousness the analogue with living systems is a simple one, for logical machines with their multiplicity of switches connecting inputs and outputs resemble the structure of a spinal cord rather than a brain We may therefore extend the image by recalling that the mechanism and function of an isolated spinal cord is also essentially logical A spinal reflex operates in such a way as to restore balance in a system perturbed by external influences an afferent signal from a sense organ is a proposition about the environment which is completed by the reflex response to the effectors Ideally, the equilibrium is maintained as perfectly as in a mathematical equation Lest it should be supposed that this definition leaves out of account the integrative, plastic properties of spinal function working models of reflexive action employing merely all or none elements exhibit well coordinated purposeful behaviour even when only two elements are included The appearance of purpose is no criterion either of intricacy or of awareness

The notion of a threshold

Consideration of spinal function as a process of logical equilibrium raises at once a problem in the analysis of living mechanisms which is of capital importance in the concept of consciousness—the notion of a *threshold* It is axiomatic that in the activation of a living tissue such as a nerve fibre the magnitude of the response is not directly proportional to the intensity of the stimulus there is a stimulus strength below which no response occurs, the threshold or limen In a mathematical or engineering context this effect would be said to imply the existence of a non linear operator This means simply that between the stimulus system and the response system is a connexion through which the relation between input and output is distorted by discontinuity in the curve relating the magnitudes of their respective values The existence of a non linear operator or threshold enormously complicates the description of a responsive system in mathematical terms A special form of operational calculus is devoted to the analysis of a class of events as simple as the closing of an electric switch Yet the closing of a switch is precisely what is needed to simulate in a machine the elementary logical operations of affirmation and denial just as in a spinal cord the abrupt firing of a neurone is the essential unit of reflexive action

We may say, therefore, that the existence of a threshold, a non linear relation between input and output, an all or none law, a yes or no rule is the prerequisite for a logical or reflexive system

CONSCIOUSNESS

This proposition leads to the formulation of a critical question about consciousness is the notion of a threshold limited to logical reflexive action or is it applicable also to behaviour which we choose to call conscious? In order to answer this question we must attempt to describe consciousness in more positive terms having so far identified it merely by exclusion

The significance of relation between sets of stimuli

We begin by suggesting that whatever else consciousness may imply it must involve the joint action of many physiological elements. It should be clear that an assembly of elements appropriate for conscious action is not merely a stack of parallel units with additive functions: the essence of the complexity resides rather in the *diversity* of afferent and efferent function, linked with access to stored information which together provide an estimate of probable significance. In order to make clear at once the objective of this sally, the final conclusion is that, in the upper levels of the nervous system, in conscious behaviour, the concept of a threshold cannot be defined in terms of stimulus strength: it must rather be *a measure of the probable significance of the relation between two or more sets of stimuli*. The sequence of genitives in this sentence is an indication of the "connectedness" of such a system: consciousness is not concerned with the response to any single event but with the connexion between series of events. The threshold of consciousness is not a scalar measure but a vectorial one in the most bewildering sense.

Such assertions as these commonly arouse an immediate protest. "Of course," the sceptic exclaims, "I can be conscious of an event: if I sit on a tack the volley of nerve impulses is the physiologic representation of a single event and I am quickly and acutely conscious of *it*, not just of its relationship to something." The answer to this objection must involve a little splitting of hairs, but it is reasonable. The "event" involved in sitting on a tack is the relatively high speed of entry of the point into the skin. You are not conscious of the point but of the speed of the point, that is of its rate of change of position—the relation between its position at one time and its position at another. Moreover, even an acutely "painful" stimulus may not be a conscious experience when there are powerful distractions. In extremes of fear, anger and lust, and in the states of ecstasy cultivated by some religious sects, even events resulting in serious mutilation may escape conscious attention. The reason suggested for such apparent paradoxes is that in such circumstances the *significance* of the event is below threshold compared with that of other contemporaneous events.

IMPLICATIONS OF "SIGNIFICANCE" IN THE PRACTICE OF ANAESTHESIA

This idea has implications which may be of some practical importance in the practice of anaesthesia. It will be recalled that in attempting to describe emotional experience in physiologic terms there was put forward long ago a proposition usually called the James-Lange theory of the emotions. This asserts that the subjective mental state identified as "emotional" arises from awareness of autonomic changes within the body produced in reflex fashion by an exciting, alarming or dangerous combination of stimuli. In cybernetic terms this would perhaps be described as a positive feedback between somatic receptors and autonomic effectors. A person who notes in himself the notorious signs of fear or rage may in consequence feel more fearful or more enraged and, unless brought under control, the system may well be expected to exhibit a literal run-away to a panic state. Now quite similar considerations may be applied to other aspects of behaviour in which the emotional or affective components are of less immediate importance. The motor

reflex response to a stimulus may itself provide the additional series of events which we suggest is required for conscious attention. Therefore the elimination of reflex responses to pain by paralysis of the motor system may so diminish the significance of a painful stimulus that it is rejected by the conscious selector, even though at the same time other events may be consciously appreciated.

The importance of the response to a stimulus in emphasizing its significance can be illustrated in a working model. This effect was discovered in the course of experiments with an electronic device intended to show the various operations required for a theory of learning by association. It was observed that when the model was adjusted to simulate a defensive conditioned reflex, the conditioned response could be self-maintaining instead of being extinguished in the absence of reinforcement. Consideration of the circuit and the conditions showed that the reason for the durability of the defensive reflex was that the motor response to the conditioned stimulus itself acted as a reinforcing unconditioned stimulus, because it was, so to say, logically inseparable from the specific or unconditioned sensory stimulus.

The physiological inference to be drawn from this analogue is that a painful or noxious stimulus may not have adequate significance by itself to evoke the somatic, autonomic and mental changes we describe as feeling pain. The experience of pain may, in certain circumstances at least, depend upon the presence of the reflex responses to the stimulus as well as the stimulus and its immediate sensory consequences. The criterion for deep surgical anaesthesia used to be relaxation, particularly in the absence of a reflex response to painful stimulation. With modern techniques a comparable state can be achieved by a combination of light anaesthesia and muscular paralysis with curariform drugs. It is suggested that this method does not merely provide the surgeon with a more tractable musculature but also deprives the patient of an essential part of conscious appreciation—his own reflex responses to the surgical assault. In normal conditions, of course, muscular paralysis only is inadequate for anaesthesia and in fact induces a peculiarly disagreeable state: awareness of the whole situation without the logically essential component of muscular participation is equivalent to a nightmare of impotent frustration. But in a state of light anaesthesia the details of the environment are effaced and the incompleteness of subjective sensation is accepted without protest.

RESPONSES TO STIMULATION IN SPECIFIC AND NON-SPECIFIC REGIONS

This argument—derived mainly from theoretical considerations—finds some support in the results of experiments with animals, but the situation is still uncertain in human beings. It has been shown by many observers (French, Verzeano and Magoun, 1953; Brazier, 1954; Arduini and Arduini, 1954; Buser and Borenstein, 1957) that when cats with implanted brain electrodes are anaesthetized the diffuse responses to stimulation are first exaggerated and then effaced. These responses, which are normally found in the secondary and non-specific regions of the cortex, depend upon the integrity of polysynaptic relays in brain stem, thalamus and cortex; they are characteristically variable and vulnerable to all influences. In contrast, the responses in the specific sensory projection areas are more resistant to anaesthesia. In fact, the mapping of cortical sensory zones by neuronography

which has usually been done under anaesthesia has yielded greatly over simplified results simply for this reason the response areas are clearly defined only when the animal is anaesthetic and thus by definition cannot in any useful sense perceive the stimulus In human beings crucial experiments are still to be performed but there is some evidence (Walter 1954 Clutton Brock and Walter 1957) that under the influence of a light anaesthetic combined with relaxants the differential vulnerability of the primary and other cortical regions can be demonstrated even when the patient is unresponsive to fairly painful stimuli such as compression of the tendons and superficial nerves At this stage the anaesthesia is deep enough for the patient to deny any memory of the experience nor are there any signs of autonomic reaction yet the electrical activity of the brain is barely outside the range of normal tranquillity and certainly displays none of the patterns identified with the early stages of anaesthesia As a practical consequence, the side effects of light anaesthesia with muscle paralysis are slight and recovery from it rapid It should be noted however that because the changes in electric brain activity are so slight the electrographic methods suggested by Bickford (1950) and by Wyke (1957) for monitoring and even regulating anaesthetic levels should be used with caution since they depend on the induction of relatively gross changes in brain activity

The physiological mechanisms involved in these peculiarly selective forms of behaviour are still somewhat obscure in human beings they are obviously particularly inaccessible since they must involve deep-seated structures rather than the cerebral cortex There is however, some suggestive evidence from animal experiments that may indicate the operation of similar mechanisms Several experimenters notably Jouvet and Hernandez Peon (1957) have discovered that in chronic preparations of cats with implanted electrodes, the state of attention leads to the selective transmission of a small number of sensory signals with concomitant blocking of other afferent signals For example during states of visual attention, the electric changes evoked in the dorsal cochlear nucleus by sounds are greatly attenuated It has also been possible to identify a state sometimes called habituation —boredom would be more apt for human beings—in which sensory signals having lost their significance by vain repetition the response at the first relay nucleus dwindles to negligible proportions Both attention the emphasis of a novel or significant association and habituation the suppression of a familiar or irrelevant one are generally highly selective It is important to note however that this selectivity diminishes rapidly with light anaesthesia and is permanently abolished by destruction of the reticular system of the brain stem These effects seem to be due to the action of a centrifugal inhibitory mechanism acting on the subcortical relays from the sensorium the input to this selector is probably derived from the information about stimulus significance arising in the cortico reticular circuits

VOLUNTARY CONTROL OF MOVEMENT

Modern conceptions of the voluntary control of movement have developed on similar lines The initiation of a voluntary movement is now considered to be the responsibility of what is called the *gamma* loop This is a complex circuit also under the influence of the reticular activating system in the brain stem which links the smallest ventral horn cells in the spinal cord with the intrafusal fibres in the

muscle spindles This system acts as a sort of detonator for the more massive *alpha* motor system and translates into readiness for movement the information collected by the significance net in the brain stem In this case again, extreme alertness may enhance or re establish functional integrity The parkinsonian patient, reduced to tremulous rigidity by the deficits and excesses in his extrapyramidal system, can abruptly recover an athletic demeanour if he be sufficiently goaded or terrified by impending catastrophe Here again the powerfully significant stimulus, supplemented by the neurohumoral action of the sympathetic nervous system super activates the reticular system and ignites the long dormant *gamma* loops (*see also* Chapter 1)

SENSITIVITY OF THE RETICULAR SYSTEM

The indispensable contribution of the reticular formation to conscious behaviour (Walter 1954) depends of course upon the web like character of its distribution through the brain—from which indeed its name is derived The wide dispersion of information from all sense organs to many brain regions is the basis of awareness and contributes also to the plasticity of brain function only in the zones of specific projection can damage or disease produce irreversible deficit To set against this the synaptic relays within the reticular system itself are exquisitely sensitive to interference It is not certain whether this is due to some specific delicacy of their organization or to the simple fact of their being connected in a cascade or series of junctions This latter explanation may be sufficient since it would seem that all signals traversing the reticular pathways must run the gauntlet of at least seven synaptic relays Now it is a matter of simple arithmetic that if an agency can reduce by one half the likelihood of an afferent impulse generating an efferent one across a synapse then if this agency influences seven such synapses in cascade, the chance of an impulse at the input to the system resulting in an impulse from its output is diminished by one half raised to the seventh power, that is by a factor of 128 In effect a cascade system of this sort is an amplifier models of similar nature demonstrate very clearly the dramatic effect of general changes in modifying the transmission characteristic when the coefficients are multiplied From this elementary calculation we can conclude that the reticular activating and controlling system is likely to be more than one hundred times as sensitive to general changes—that is particularly blood borne agencies—as any individual nerve cell The differential will be even greater if the comparison is with parallel connected systems and this may well be the case in the cerebral cortex

The high vulnerability of the basal and midline structures is seen particularly clearly in two clinical conditions the type of epileptic attacks now referred to by clinicians as centrencephalic seizures and in concussion In both these states consciousness is lost abruptly and completely and there is often also some degree of retrograde amnesia In both there is ample evidence of disturbance localized to the basal and central regions of the brain In contrast severe and extensive damage or disease in the cerebral cortex or subcortical white matter rarely has any dramatic effect on consciousness or memory There have been cases in which nearly a whole hemisphere has been ablated, by projectiles or by surgical intervention with no disturbance of awareness or orientation

Applying these ideas to the action of anaesthetics it seems likely that in the usual

doses anaesthetic agents have relatively little effect on the cerebral cortex The same is true of most other drugs acting on the central nervous system, alcohol, the adrenergic amines, the ataractics and narcotics have all been shown to exert their action by way of the non specific afferent systems in the thalamus and brain stem

IMPORTANCE OF SIGNIFICANCE RATHER THAN STRENGTH OF STIMULI

Even in the more remote domain of experimental psychology, there is ample evidence that conscious attention and comprehension are dependent on the significance rather than on the strength of a stimulus Many experiments have shown that normal subjects can respond objectively to significant signals which are considerably weaker than those they can just ' consciously" perceive if the signals are isolated or trivial This phenomenon has been given the paradoxical name ' sub threshold perception or sub ception, it can be used legitimately to discriminate between signals which are indifferent and those which for some personal reason, are significant for a particular subject The effect has even been claimed to be of value in advertising, the name of a product flashed on a cinema screen for one twenty fifth of a second—too brief an exposure to be noticed consciously—may later be associated unconsciously with that commodity, thus significantly increasing the likelihood of one particular brand being sought by members of the captive audience Such observations are reminiscent of the peculiar forms of behaviour classed as hypnosis here too the narrowing of attention by hypnotic suggestion and separation of sensory modality can be described in terms of altered significance Many anaesthetists must have wondered whether inadvertent hypnosis may not play some part in the modern techniques of induction when the absolute level of chemical anaesthesia may be much less profound than in the early days Even on quite general grounds it seems probable that much of our everyday behaviour is determined by the interaction of many signals, both exogenous and endogenous, which are well below the threshold of conscious identification, yet are effective in their joint implication

CONCLUSION

We began by supposing that consciousness was an attribute of a complex system of communication and went on to distinguish probabilistic from logical reasoning This distinction is more than verbal and has serious consequences in any attempt to define a physiologic basis for conscious behaviour, since the study of statistical relations in a complex interacting system requires unconventional tactics The inclusion of consciousness in the domain of experimental science though it may be stigmatized as metaphysiology is a serious challenge to technicians and theoreticians, since there is a prospect of exploring some of the crucial problems of human existence

I wish to acknowledge gratefully the advice and assistance of Dr J Clutton Brock in the compilation of this chapter

REFERENCES

Arduini A and Arduini M G (1954) *J Pharm exp Ther* 110 76

Bickford R G (1950) *EEG clin Neurophysiol* 2 93

Brazier M B A (1954) In *Brain Mechanisms and Consciousness* Ed by Adrian Bremer and Jasper Oxford Blackwell

Buser P and Borenstein P (1957) In *Conditionnement et Réactivité en Electro-encephalographie* Ed by Fischgold and Gastaut Paris Masson

Clutton Brock J and Walter W Grey (1957) Unpublished observation

French J D Verzeano M and Magoun H W (1953) *Arch Neurol Psychiat* 69 519

Jouvet M and Hernandez Peon R (1957) In *Conditionnement et Réactivité en Electro-encephalographie* Ed by Fischgold and Gastaut Paris Masson

Walter W Grey (1954) In *Brain Mechanisms and Consciousness* Ed by Adrian Bremer and Jasper Oxford Blackwell

Wyke B D (1957) *Anaesthesia* 12 157

CHAPTER 4

ANALGESIA AND SEDATION

JOHN BEARD

INTRODUCTION

Suffering may be physical or mental, increasing study has not more clearly separated the two but has emphasized their close relationship So also analgesia and sedation overlap but, in the main the first part of this chapter is concerned with analgesia and the second with sedation The field is so wide and progress so rapid that this attempt to show the directions in which recent work has been carried out can only be selective, and incomplete

Recovery wards in which the immediate post anaesthetic stage is supervised by anaesthetists are increasing our interest in pain control and sedation and provide opportunity for training junior staff and for controlled trials of agents and methods Recognition of anaesthetists special interest and skill in use of analgesics and sedatives has led to more frequent requests for their help in dealing with pain But anaesthetists have not played as large a part in organizing and running pain clinics as some had hoped Few have the time or ability to undertake such work moreover anaesthesia has no exclusive rights in the treatment of pain This is in the first place often by surgery or by other methods aimed at the cause of pain

Anaesthetists can provide nerve blocks which if successful may be followed by neuro surgery or may be repeated using such agents as alcohol or phenol The latter in spite of inherent hazards have a small place though their use in an anxious and pain weary patient demands patience extreme gentleness and skill It is a matter for regret that the excellence of general anaesthesia and the preference of patients and surgeons has reduced the opportunities for learning and practising the various techniques for nerve blocking in the course of ordinary theatre work

ANALGESIA

It is generally agreed that pain in man has two components There is the perception of pain and there is the reaction to this original sensation (Beecher, 1956a)

The measurement of pain

The threshold above which pain can be perceived by man has been the subject of much study, particularly by the radiant heat method of Hardy, Wolff and Goodell (1940) These workers reported consistent and reliable results which have

not however, been found by others who quote very variable figures (Chapman, 1944 Leduc and Slaughter 1945 Slaughter and Wright, 1944) Similar variation in the response to electrical stimulation of skin or tooth pulp and to the von Frey hair technique is usual Beecher (1956b) has pointed out that the pain threshold in man is not constant from day to day and that it is not in fact a 'pure' perception but is already subject to psychic processing *before* awareness is achieved He has drawn attention to the suggestion of Wikler (1944, 1945) that the pain sensation probably reverberates in the internuncial neurones before arriving at the level of consciousness there being in existence an anatomical network in which such changes in intensity of pain impulses can occur before they reach the cortex It seems probable then that, in spite of much stimulating and valuable work by Hardy and his co workers, experimental pain is subject in a varying degree to such modification even in trained intelligent volunteers, and that any assessment of analgesic drug potency obtained in this way cannot be taken as solely due to alteration in the threshold of the perception of pain but is also a function of the drug s effect on the psychic processing It is interesting to note that Harris and Worley (1953), using the electrical stimulation of the tooth pulp in man, have reported significant analgesic effects from a proprietary combination of amphetamine with antipyretic analgesics The latter have been repeatedly found to be without threshold raising effect, but the marked effect of amphetamine on mood is generally agreed and would seem to provide an explanation of the experimental findings and reinforces the view that calm detached observers in the scientific atmosphere of the laboratory may have their responses to pain altered by changes in their mood Such changes in mood while they may explain variation of threshold from day to day are likely to be less on any one day Taking this into consideration and working with paid, trained volunteers Keasling and Gross (1956) using the Wolff Hardy Goodell technique for measuring analgesia found satisfactory correlation with clinical assessment in a double blind and statistically controlled experiment with alphaprodine pethidine and another potent narcotic The attempt has been made to calibrate the patient s experience of pain by comparing it with the radiant heat stimulus of the Wolff Hardy Goodell technique using an arbitrary unit of pain, the dol This method was used by Javert and Hardy (1951) to assess the effectiveness of analgesics on labour pain in a relatively small series The technique, while it has limitations and is open to criticism nevertheless has value and interest the paper illustrating the ability of moderate doses of analgesics to reduce the intensity of a pain as experienced by the patient without raising the threshold of skin pain

Nor is it possible to measure the threshold of pain perception as a 'pure entity in the experimental animal It would seem probable that to an animal all pain is what a human would regard as pathological and to which an intellectual response cannot be expected it elicits conditioned responses which can however form the basis of a crude but useful method for detecting potent analgesics

Wound pain

Pathological or wound pain in man is a subjective experience peculiar to each individual who alone perceives it and on the description of whose suffering we are dependent for its assessment Some have much cause for pain and appear

to suffer little while others have a maximal central response Post operative pain has been studied in the course of work to assess analgesic drug potency Using this constant supply of cases, which have been subject to fairly standardized trauma it has been found that even the uncontrolled clinical trial, if on a large enough scale is at least as accurate as are the various laboratory pain threshold techniques in human volunteers and experimental animals During the last few years using pathological or post operative pain, methods of assessment and comparison which need fewer cases and are more satisfactory have been described by Keele (1948), Hewer and his colleagues (1949), Keats and Beecher (1950) and Robson and Keele (1950) The Harvard group, led by Beecher has developed these methods with great care and thought using, however, particularly strict methods of control (Keats and Beecher, 1952) Nevertheless, it is claimed that comparable results may be obtained using the clinical trial method on large numbers, multiple co variant statistical analysis being applied to the data (Gross and Schiffrin, 1955)

Gruber and his co workers (1956) summarized the general methods of studying the potency of analgesic drugs as follows (1) animal tests, (2) trained volunteers working on pain threshold (3) pain reduction in patients with chronic pain and (4) reports from patients with chronic pain concerning their comfort

Although all these will give information on the effectiveness of potent narcotics, the authors pointed out that weaker agents such as codeine or salicylate are much more difficult to evaluate and they consider that the last method is unquestionably the best The emphasis has thus shifted away from the laboratory assessment of analgesics in man and animals to the study of drug action on the patient and this may be employed in the course of their routine work by those who are without laboratory facilities Any such trial must be carefully planned using where appropriate random choice of drugs double blind testing of both patient and observer a placebo and if side effects are being assessed, it is important to use equipotent doses of various drugs Finally expert statistical control of the results is mandatory *

Some of the points which have received emphasis as the result of this greater interest in pain are of importance in the use and in the clinical testing of analgesic drugs After operation there is a great variation in the apparent need for analgesics In a series of 237 post operative patients 44 per cent did not complain of pain (Papper Brodie and Rovenstine, 1952) Of this series 108 patients had undergone intra abdominal or intrathoracic surgery, and of these 27 per cent did not complain This contrasts with those who had only surgery of superficial tissues and of whom 58 per cent made no complaint Many of the complaints after operation are not of actual pain from the wound but of restlessness sleeplessness headache, enforced immobility discomfort from tubes splints or of urinary difficulty Although many of these complaints stop after the administration of a narcotic this is not the best treatment for anoxia or a distended bladder nor an adequate substitute for nursing care Using morphine Keats (1956) found that

* A recent suggestion by Paton (1957) for a relatively simple laboratory technique is likely to be exploited in the near future He has shown that the isolated guinea pig intestine provides a test object for analgesics with closer analogies to the central nervous system than might be expected and concludes that it is striking how far the nervous system of the gut corresponds in its reactions to those of the central nervous system

aching or visceral pains were relieved in 74 per cent of cases while the sharp stabbing pains due to coughing or moving were helped in only 44 per cent of cases This latter accords with the finding that morphine in 15 milligram dosage does not alter the brief jabs of pain experienced in laboratory tests of pain in man Such pain from the actual wound has been treated by the repeated instillation of local anaesthetic into plastic tubes stitched into the incision The method has not been generally adopted probably because of the risk of local complication and because it could not be expected to give relief to the more general discomforts such as bowel pain (Lewis and Thompson, 1953)

Reaction to pain

In a post operative pain study (Keats, 1956) it has not been found possible to correlate the type of patient with the degree of pain experienced after operation It may well be that an elaborate psychological assessment as in the case of the placebo reactors (*see below*) would reveal significant factors not obvious on ordinary clinical examination Less attention is likely to be given to pain by patients living active and happy lives full of interest than in the case of the lonely and psychologically impoverished, but White and Sweet (1943) pointed out that one who has appeared active and happy for years may have hidden fears and a neurotic pattern of reactions which are revealed when he is immobilized by painful illness Furthermore it has recently been re emphasized that the abnormal or psycho pathic type reacts abnormally to drugs (von Felsinger, Lasagna and Beecher 1955 Lasagna, von Felsinger and Beecher, 1955) For example, the standard response to amphetamine is euphoric, the minority response is sedative in the case of morphine dysphoric, the minority euphoric Similarly, pentobarbitone is usually sedative but to a few it is stimulating In each case the authors considered the minority response was predominantly given by the psychopaths in the group investigated The importance of the meaning or significance of pain is very real To a civilian peacetime casualty injury is a threat to his employment and his security it is a source of anxiety and 80 per cent of patients asked for pain relief (Beecher 1956b) On the other hand Beecher (1946) questioned recently wounded men after their removal from battle to comparative safety and found that only 25 per cent wanted pain relief They were thankful to escape alive from the battlefield and the wound was the cause for their probable return home and was for that reason acceptable

Placebo reactors

When a patient is in pain as in the post operative period the administration of a drug cannot but be significant and exert powerful suggestion In these circumstances the placebo reaction is likely to be more frequent than in a laboratory experiment Indeed Fischer and Dlin (1956) pointed out that all humans however maturely adjusted may as a result of suffering or longing for the relief obtain a placebo reaction regard less of the nature of the placebo Placebos have been noted by Beecher (1956c) to be more effective in relieving a stressful situation when the stress is severe he quoted Cleghorn and others (1950) who found that a placebo given to patients with anxiety results in an increase of adrenal cortical activity of greater degree in those with severe as opposed to those with mild anxiety In the ordinary post operative pain study the

placebo reactor is difficult to pick out from the non reactor The Harvard group in studying this problem (Lasagna and his colleagues 1954) found that there were differences in attitudes habits background and personality but that these were not obvious on ordinary clinical examination and could be found only by extensive and careful psychological investigation The large number of placebo reactors (about 30 per cent) in an investigation tends to obscure the results and elimination of these reactors tends to sharpen the focus and may make more evident a particular drug effect (Beecher 1955) Not all the reactions to a placebo are pleasant and there have been reports of toxic rashes collapse diarrhoea and angioneurotic oedema (Wolf and Pinsky 1954) Indeed it seems that the assertion that human beings are suggestible has as a result of much hard work now been proven and may be accepted by scientific workers

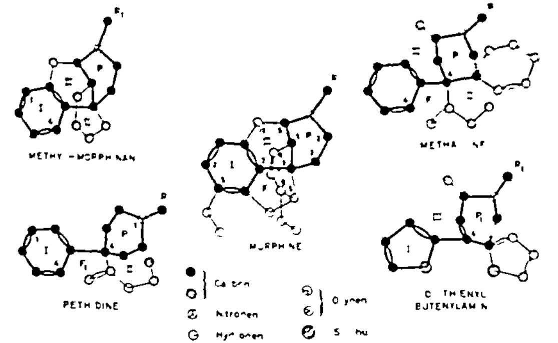
Salicylates

Some drugs such as atropine in colic act locally in the organ or tissue in which the pain arises These are not considered analgesics although they relieve pain Analgesics are considered to be those drugs which, acting on the central nervous system relieve pain without significantly impairing consciousness There are those who do not now regard aspirin and salicylates as true analgesics as they have no effect on pain threshold and are thought by some to act by reducing oedema in the tissues Support is lent to this theory by the fact that they are most effective in integumental pain of an aching type leaving sharp, severe pain and visceral discomforts unaffected (Wikler, 1950) Recently Keele (1957) has found that salicylates have some inhibiting effect on the pain producing substance of plasma Of interest to anaesthetists is the hypoprothrombinaemia which may follow really intensive salicylate therapy such as may be needed in rheumatic fever or in the prophylaxis of gout This danger may be avoided by giving 1 milligram of synthetic vitamin K analogue per gramme of salicylate Other toxic effects for example tinnitus nausea and vomiting are largely central since they may follow intravenous administration and are manifest as the plasma concentration approaches 35 milligrams per 100 millilitres (Graham and Parker, 1948) The hyperventilation which occurs may be the result of direct stimulation of the respiratory centre or of a true metabolic acidosis and is a main symptom of over dosage Brodie and Axelrod (1949) showed that phenacetin and acetanilide both owe their effects to N acetyl p aminophenol a breakdown product which unlike the original substance is free from risk of methaemoglobinaemia This compound may in the case of aspirin intolerance be a useful but no more effective alternative Although during the post operative period analgesics are usually given parenterally owing to gastro intestinal disturbance the oral route has obvious advantages especially in the treatment of chronic pain Beecher and his co workers (1953) using the latter part of the post operative period found 10 grains of aspirin more effective than a placebo while on the other hand $\frac{1}{6}$ of a grain of morphine and 1 grain of codeine when given by mouth gave decidedly inferior relief It is of interest that recent studies using radioactive carbon in the methyl group of codeine (methyl morphine) have shown that it is demethylated in the bowel Probably much of this drug s effect is due to the released morphine (about 10 per cent of the codeine being absorbed Many of the synthetic narcotics are well absorbed from the gut notably methyldihydryomorphinone (Metopon) levorphanol and methadone

The greatest need today is probably not for a more powerful analgesic but for an orally given drug which would fill the gap between the mild analgesic-antipyretic group and the more potent narcotics. The latter group are all, with the probable exception of nalorphine (*see below*), drugs of addiction.

Morphine-like analgesics

Eddy, Halbach and Braenden (1956) described the chemical features possessed in common by the morphine-like analgesics. These features are also characteristic of the compounds which produce morphine-like addiction. They are (a) tertiary nitrogen, (b) a central carbon atom none of whose valencies is connected with hydrogen, (c) a phenyl group isosteric with the phenyl which is connected with the central carbon atom, and (d) maximum activity when the central carbon atom is connected with nitrogen by a two-carbon chain. The same workers in an earlier paper (Braenden, Eddy and Halbach, 1955) discussed the molecular structure of these compounds. Since 1902 the phenanthrene structure has been considered to be a characteristic of the morphine



Drawing of molecular models illustrating the "pseudo-piperidine ring" structure in morphine, morphinan, pethidine, methadone and a dithienylbutenylamine
(*After Rados-Thomas, 195[illegible]*)

group of analgesics. With the discovery of pethidine, a 4-phenylpiperidine, by Schaumann in 1939 the morphine-like characteristic was linked by him to the 4-phenylpiperidine system which can be seen in the morphine molecule. When methadone, which did not contain a piperidine ring, was discovered, the narcotic "essential group" was simplified by him to (a) a quaternary carbon atom, (b) a benzene nucleus attached to (a), and (c) a tertiary amine group separated from that carbon atom by two methylene groups. These features are common to morphine, pethidine and methadone. Further modification to fit the "essential group" to the dithienylbutenylamines were made but it was later suggested (Gero, 1954) that in both methadone and the dithienylbutenylamines part of the molecules was in a position resembling a piperidine ring

and Eddy Halbach and Braenden (1956) showed photographs of molecular models which illustrated the pseudo piperidine ring structure in morphine morphinan pethidine methadone and a dithienylbutenylamine The diagram illustrates the point

Nature of morphine like effect

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Potentiating drugs

Other methods of achieving this aim are being investigated and it has been found that neostigmine potentiates the analgesia of morphine (Szerb and McCurdy 1956) without increasing its cerebral concentration similar claims have been made for pyridostigmine (Mestinon) These drugs are cholinergic and have a helpful tendency in counteracting the action of morphine on the gut A striking potentiation of morphine action is reported (Chen 1956) to result from 1 dimethylamino 2 phenyl 3 methyl pentane hydrochloride a compound having some structural resemblance to methadone This has only been used in animals and may not be applicable to man as it produces a diuresis It does not potentiate barbiturates,

thus contrasting with chlorpromazine which while it does so markedly has a less clear cut effect with morphine Chlorpromazine has no analgesic effect in ordinary dosage but can be useful in the treatment of pain, particularly of malignant disease (Dundee 1957) In some patients but by no means all, it provides sedation and relief from anxiety and may often allay completely the nausea and vomiting due to morphine administration It has been claimed that chlorpromazine produces an indifference to pain the effect being likened to leucotomy The same analogy was drawn in the case of barbiturates by Keats and Beecher (1950), who claimed that pentobarbitone sodium given intravenously relieved post operative pain in 50 per cent of cases in contrast to saline solution which gave a placebo effect in 20 per cent, morphine being effective in 80 per cent Wikler and his co-workers (Hill, Belleville and Wikler, 1955) doubted the efficacy of barbiturates as analgesics and recalculated Keats and Beecher s figures showing that while comfort as judged by *observer* was 38 8 per cent pain relief as judged by *patient* was obtained in only 26 8 per cent a figure little better than that given by a placebo These results are more in accord with clinical experience

The attempt to secure adequate depth of analgesia without depression of respiration by adding N allyl normorphine to morphine has not been entirely successful (Eckenhoff Hoffman and Dripps, 1952 Payne, 1954) The addition of levallorphan to levorphanol in chronic pain (Cullen and Santos, 1954) or to alphaprodine as a supplement to nitrous oxide (Swerdlow, 1957) is rather more promising Similarly amiphenazole (Daptazole) has been used to counter the respiratory depression of really large doses of morphine (100–130 milligrams) in malignant disease, and has been employed (as has nalorphine and levallorphan) to combat neonatal apnoea (Holmes 1956) A tuberculous woman who had become addicted to morphine and pethidine was treated by amiphenazole for three days after which she has remained apparently free from addiction for ten weeks (Ballantine 1957) This startling finding if confirmed is certainly important and further investigation might be most profitable

SEDATION

Much distress both physical and mental is relieved by depression of consciousness In general there is a progression sedation leading to sleep and eventually to anaesthesia This sequence which largely through its effect on the psychic component of the pain experienced somewhere includes analgesia is the result of alterations in the level of awareness Consciousness or the waking state is thought to be dependent on a stream of impulses radiated to the central hemispheres from an area in the brain stem and hypothalamic region which has been described by Magoun (1950) as the reticular activating system (Fig 9) This system has a multisynaptic structure as is also found in the central cortex and it is suggested that these areas are those largely concerned in the anaesthetic state (French Verzeano and Magoun 1953 *see* Chapter 3) Even a small dose of ether or of barbiturate inactivates this system in the experimental animal and for this reason its recognition was delayed until electroencephalography was carried out in the curarized and locally anaesthetized monkey

Site of action

Recent studies made on conscious patients in whom fine silver electrodes had

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Dictionary as "freedom from disturbance of mind" or as "stoical indifference" Of these ataractics many are derived from drugs with which anaesthetists are already familiar, and some are already in use in pre operative and post operative medication The antihistamine preparation promethazine (Phenergan) has been fairly widely used as a sedative (Beard 1954) It prolongs the action of barbiturate perhaps by increasing the permeability of the blood brain barrier (Lightstone and Nelson 1954) Its sedative effects are exerted below cortical level judging from the epileptiform convulsions which are occasionally released during its use—a liability shared with many of its derivatives The first of these, chlorpromazine has already a considerable literature It has been followed by pecazine (Pacatal) a piperidyl phenothiazine promazine (Sparine) and by acetylpromazine (Notensil) These latter are without the toxic chlorine atom in the phenothiazine ring and have so far less often been the cause of liver damage but pecazine at least can still cause agranulocytosis These dangers seen only when administration is continued over a period are accepted in view of the valuable sedation in psychoses, particularly manic excitement The delirium of the toxic drugs or states is usually controlled, but the evidence of skin sensitization in those handling the drug is very high and should be remembered by anaesthetists Other sedative antihistamines diphenhydramine (Benadryl) and meclozine (Bonamine Ancolan) have led to the development of the ataractics Covatin and hydroxyzine (Atarax) respectively These while mainly used in the neuroses are being tried in premedication Reserpine one of the rauwolfia alkaloids is a yohimbine derivative and exerts marked sedative effects

The most widely used ataractic meprobamate (Miltown Equanil) was derived from mephenesin and like this drug it produces muscular paralysis in large doses It may be the cause of drug rashes and occasionally of profuse diarrhoea since it is an urethane, blood dyscrasia is a possibility on theoretical grounds Given in single doses of 400–800 milligrams it seems to produce relaxation and to encourage sleep, and has therefore been used in premedication It would seem particularly indicated in tense anxious patients or in those with pain due to muscle spasm it has no real anticonvulsive effect and except that the price is about twenty times greater it is comparable with short to medium acting barbiturates but since it is less poisonous may be more safely used for potentially suicidal patients

There is however a real qualitative difference in the sedation of the ataractics as compared to the barbiturates and an experiment by Walaszek and Abood (1956) is illuminating. Siamese fighting fish (Betta splendens) were immersed in a dilute solution of various drugs Reserpine chlorpromazine meprobamate antihistamines analgesics and hypnotics were among those tested Whereas hypnotics and analgesics had little effect the ataractics and the antihistamines completely blocked the natural fighting responses of these pugnacious fish. Similar experiments with the Russian Red Snapper and the Chinese Swordtail have been suggested

In general, the ataractics reduce tension and overactivity in the anxious This may be beneficial particularly to those in contact with the patient, but it is possible that this very overactivity is the means by which the patient expresses his inner tension What is more not everyone likes being sedated however, since more than 35 million prescriptions for meprobamate are said to have been dispensed in the

been previously placed at various levels in the brain (Heath, 1954), have shown that the electrical changes of sleep appear first in the subcortical zone at a time when clinically the patient feels only drowsy Later, with the onset of actual sleep the electrical changes spread into the overlying cortex Similar electrical changes followed the administration of amylobarbitone sodium, but with pheno barbitone it was noticeable that the cortex was involved to a greater extent, this being in accord with the well recognized effectiveness of the latter drug on epileptiform convulsions, which are regarded as due to cortical disorders King (1956) working with cats has produced evidence confirming the work on the site of action of some anaesthetic and sedative drugs It would appear that barbiturates in general alter the threshold of arousal by preventing the stimulation of the reticular formation which arrives *via* the collaterals from the classical somatic sensory pathway (Fig 9)

With small doses of barbiturates sensory cortical responsiveness was not impaired, and indeed the responses from the diffuse thalamic projection system

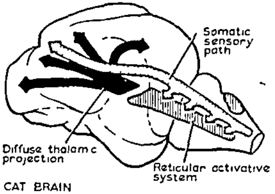


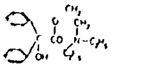
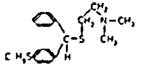
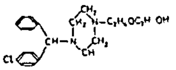
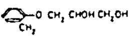
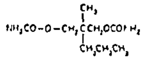
Fig 9 —Reticular activating system

freed from the inhibition due to reticular formation activity were increased as shown in the electroencephalograph by spindling Ether, on the other hand, depressed both the reticular formation and the activity responsible for 'spindling Mephenesin which is a non anaesthetic interneurone depressant does not block the reticular activating system as do small doses of ether or barbiturates King suggested, therefore that it is improbable that the multisynaptic organization *per se* is the explanation of the susceptibility of the mechanism to anaesthetic agents but she agrees that her data support the hypothesis that these drugs produce sleep by selective depression of the extralemniscal reticular tracts by which sensory impressions contribute to cortical arousal Ether given in doses so small as not to impair consciousness and thus presumably not blocking the ascending reticular system can produce analgesia Belleville and Artusio (1955) suggested that in this case a block occurs either at some point in the cortex or between the thalamus and the cortex so that pain is not appreciated

Ataractics

A drug which is sedative without producing drowsiness has uses especially in abnormal mental states Mephenesin is claimed to be such a drug and was the forerunner of a class of drugs popularly known as tranquillizers to which the name ataractic has been given (Table I) ataraxy is defined in the Shorter Oxford

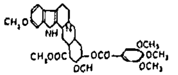
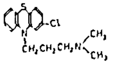
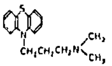
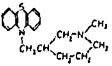
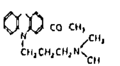
TABLE I—*continued*

Group	Name and Trade Name	Chemical Description	Structure
Benzhydrol Derivatives	Benactyzine (Suavitol Nutinal Lucidil Cevanol)	Dimethyl amino-ethyl benzilate	
	Covatin	Butyl thio diphenyl methyl-dimethyl amino ethyl sulphide	
	Hydroxyzine (Atarax)	Chloro diphenyl methyl hydroxy ethoxy ethyl piperazine	
Propanediols	Mephenesin (Myanesin)	Methyl phenoxy propanediol	
	Meprobamate (Miltown Equanil)	Methyl propyl propanediol dicarbamate	

(After Hartley (1956) by courtesy of the Pharmaceutical Journal)

serotonin levels in the brain, but it has been suggested that chlorpromazine suppresses adenine triphosphate utilization to the greatest extent in the reticular formation (Grenell Mendelson and McElroy, 1955) or that it may act by inhibiting noradrenaline which serves as one of the neuro humoral transmitters Chlorpromazine is a true potentiator since it will re induce sleep in animals which have recovered from barbiturate or alcohol sleep, without interference with the metabolism of these drugs (Brodie and his colleagues 1955) In contrast, the sleep prolonging effect of iproniazid and also of propyl trasentin, which have no hypnotic effect of their own is apparently due to their inhibition of oxidase systems (Fouts and Brodie, 1956) including the mono oxidase which destroys serotonin It is of interest that Fastier Speden and Waal (1957) have found that the sleep time of chloral hydrate is significantly prolonged by a variety of compounds including serotonin adrenaline methoxamine histamine ergotamine yohimbine and atropine most of which are known to lower body temperature It is suggested that some at least of the drugs which prolong hypnotic effect do so by virtue of hypothermic action So also potentiation of barbiturates may be associated in some circumstances with the lowering of temperatures which may result from the use of chlorpromazine or reserpine (Lessin and Parkes 1957) Experimentally

TABLE I
CHEMICAL STRUCTURE OF THE ATARACTICS

Group	Name and Trade Name	Chemical Description	Structure
Rauwolfia Alkaloids	Reserpine (Serpasil Sandril Quiescin)	Derivative of yohimbine	
Phenothiazine Derivatives	Chlorpromazine (Largactil Thorazine)	3 Chloro dimethyl amino propyl phenothiazine	
	Promazine (Sparine)	Dimethyl amino propyl pheno thiazine	
	Pecazine (Pacatal)	Methyl piperidyl phenothiazine	
	Acetyl promazine (Notensil)	Acetyl dimethyl amino propyl phenothiazine	

United States of America during 1956 this seems to be a minority response, but it should be remembered when premedicating patients

Potentiation of barbiturates

Although large doses of barbiturates reduce cerebral oxygen consumption no such effect occurs with reserpine or the phenothiazine derivatives They do however markedly potentiate the action of barbiturates without apparent change in cerebral oxygen consumption (Fazekas Albert and Alman 1955) Reserpine lowers the level of the brain serotonin (5 hydroxytryptamine) an effect which persists for a few days after reserpine is stopped and is no longer demonstrable in the brain tissue It is noteworthy that the serotonin level in the rabbit brain stem is three times that of the rest of the brain and that in mice serotonin potentiates barbiturate action as also does reserpine (Pletscher Shore and Brodie 1955) Barbiturate action is also potentiated by iproniazid which is known to inhibit the enzyme amine oxidase which destroys serotonin

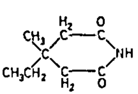
Since reserpine potentiates barbiturate action it is a little surprising in view of its increasing use that no case of susceptibility to barbiturates from this cause has as yet been reported The phenothiazine derivatives have no known effect on

Thus the type and amount of sedative and analgesic drug must, in many cases, depend on the adequacy or otherwise of aftercare

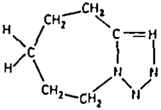
Barbiturates

The barbiturates are still the most widely used sedatives, costing in England about £2,000,000 a year and being responsible for more than 6,000 cases of poisoning yearly, of which over 500 are fatal

The results of treatment in large series of such intoxications (Nilsson 1951 Locket 1956) have been better when analeptics or other antagonists have not been employed However it will probably be found especially where skilled and specialized medical and nursing care is not available that there is room for discreet use of such drugs in order to lessen the depths of coma thus improving ventilation and allowing the return of the protective pharyngeal and laryngeal reflexes Bemigride (Megimide) β-ethyl β methyl glutarimide is the example of current interest (Shulman and his colleagues 1955) Its formula can be drawn so that it somewhat resembles leptazol (pentylene tetrazol Cardiazol) Like the latter it can cause convulsions and apparently owes its effect on barbiturate coma to its analeptic qualities



BEMIGRIDE



LEPTAZOL

Haemodialysis by an artificial kidney is many times more effective than the human kidney in removing barbiturate from the blood and is at present the only available known method of producing a rapid blood clearance such measures as forced diuresis and cerebrospinal puncture doing more harm than good

Chronic intoxication recognized as a problem in Germany and in the United States of America resembles in many ways chronic alcoholism It has been found that about six to eight times the normal dose of barbiturate taken for a few weeks may be followed by addiction and a dependence sufficient unless withdrawal be gradual to produce serious abstinence symptoms which may include convulsions status epilepticus and even death Kjaer Larsen (1956) has reported psychoses in cases of barbiturate addiction who had been treated with bemigride but the analogy to the withdrawal symptoms in morphine addicts when given allylnormorphine though tempting cannot yet be justified The drugs most favoured by psychopathic addicts are those of the short acting group such as quinalbarbitone (Seconal) which provide the more abrupt change of mood which is craved

Non barbiturate sedatives

Perhaps these dangers are the reason for the development of a number of non barbiturate sedatives during the last few years These seem to have few advantages in routine practice to compensate for their high price and since they are efficient hypnotics it is a matter of time before they are misused by the unstable

Methylpentynol (methylparaffinol Somnesin Oblivon Dormison) is already well known as a useful mild sedative A closely related chlorinated carbinol

it has been found that a fall in body temperature of 10° C increases barbiturate sleep time from 7 to 60 minutes and it may be suggested that chlorpromazine and reserpine by reducing body temperature slow the rate of enzymic detoxication of barbiturates and thus have a mode of action in common with propyl trasentin, which inhibits the detoxifying enzyme directly (Axelrod and his colleagues 1954) No completely coherent theory of the mode of action of these drugs is yet available but the subject is arousing great interest and has recently been reviewed by Fazekas Toupin and Alman (1956)

The need for sedation

It is true that pre anaesthetic visits can do much to establish confidence and thus reduce the need for sedation, but many patients still fear the anaesthetic as much as or more than the actual operation It is unfortunate that the use of respiratory depressants is inadvisable before ether or cyclopropane, as apprehension is especially common where induction by face mask is the usual practice In those circumstances many recommend only a small dose of barbiturate as sedative which should be given intramuscularly rather than by mouth Although this may produce some euphoria and relaxation it does not compare with the effect of a nar cotic in reducing anxiety associated with anticipation of pain (Hill Belleville and Wikler 1955) Cohen and Beecher (1951) state that on principle morphine and similar agents should not be used because of their power to produce euphoria except in conjunction with the treatment of severe pain or in patients dying with terminal cancer Presumably this is on account of the greater risk of addiction and the more extensive use of ether where they work Others on the contrary might feel that euphoria is needed in some circumstances and that premedication but rarely results in drug addiction The increasingly common sequence of intravenous barbiturate followed by nitrous oxide and oxygen necessitates vene puncture which is often feared especially by children furthermore since nitrous oxide is a weak agent until saturation is complete it is at the beginning of anaesthesia that analgesics are especially needed and to incorporate these in the premedication of healthy patients is not unreasonable Premedication induction and maintenance of anaesthesia ideally should fade imperceptibly one into another, and whether these drugs are given orally or hypodermically in the ward or intra venously in the theatre is a matter for individual judgment in each case Siker (1956) in reviewing the analgesic supplementation of nitrous oxide pointed out that this practice has made possible a much wider use of the gas which in turn has resulted in the acquisition of greater skill in its handling and hence paradoxically has decreased dependence on these adjuvants

Although narcotics reduce pulmonary ventilation to a greater extent than do the barbiturates this is of little consequence during anaesthesia since we are now accustomed to assist respiration when necessary After operation a narcotic is in any case often indicated to allay discomfort Here the resulting depression of respiration and cough reflexes may be held responsible for atelectasis, but on the other hand it must be remembered that although such a patient may feel less urge to cough when instructed to do so bronchial clearance is often more effective when anxiety is reduced and analgesia afforded by a narcotic indeed it is not uncommon to precede physiotherapy after thoracic surgery by such a drug

While these newer drugs can certainly be useful in special circumstances they have limitations and unwanted side effects Some are notably free from respiratory depression, but their place in anaesthetic practice is not yet certain and they are perhaps best regarded as the promising forerunners of other and better drugs

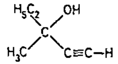
Reference has been made to pharmacological work in another direction which may prove fruitful Sedatives and narcotics with which there has long been familiarity can have their action increased by a variety of new agents, some of which may act by inhibiting enzymes which are concerned in the breakdown of the drug in the brain tissue In this way drug action may be enhanced in the brain allowing smaller dosage and hence less unwanted side effects elsewhere in the body

Thus progress in anaesthesia depends largely on pharmacology Indeed, a wide knowledge of drugs has become part of the grounds upon which anaesthesiology claims recognition as a specialty, but the title "doctor must continue to be justified by our wisdom in their use

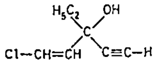
REFERENCES

Ballantine J D (1957) *Lancet* 1 251
Beard A J W (1954) *Proc R Soc Med* 47 407
Beckett A H and Casy A F (1954) *J Pharm Lond* 6 986
Beecher H K (1946) *Ann Surg* 123 96
— (1955) *J Amer med Ass* 159 1602
— (1956) Presentation at 17th Meeting of Committee on Drug Addiction and Narcotics National Research Council Washington D C
— (1956a) *J chron Dis* 4 11
— (1956b) *J Amer med Ass* 161 1609
— (1956c) *Amer J Med* 20 107
— Keats A S Mosteller F and Lasagna L (1953) *J Pharmacol* 109 393
Bein H S (1956) *Pharmacol Rev* 8 435
Belleville J W and Artusio J F (1955) *Anesthesiology* 16 379
Braenden O J Eddy N B and Halbach H (1955) *Bull World Hlth Org* 13 937
Brodie B B and Axelrod J (1949) *J Pharmacol* 97 58
— Shore P A Silver S L and Pulver R (1955) *Nature* 175 1133
Chapman W P (1944) *Psychosom Med* 6 252
Chen J Y P (1956) *J Pharmacol* 117 451
Cleghorn R A Graham B F Campbell R B Rublee N K Elliott F H and Saffran M (1950) In *Proc First Clin ACTH Conf* Philadelphia Blakiston
Cohen E N and Beecher H K (1951) *J Amer med Ass* 147 1664
Cullen S C and Santos C C (1954) *Arch Surg* 69 410
Dundee J W (1957) *Brit J Anaesth* 29 28
Eckenhoff J E Hoffman G L and Dripps R D (1952) *Anesthesiology* 13 242
Eddy N B Halbach H and Braenden O J (1956) *Bull Wld Hlth Org* 14 353
Fastier F N Speden R N Waal H (1957) *Brit J Pharmacol* 12 251
Fazekas J F Albert S N and Alman R W (1955) *Amer J med Sci* 230 128
— Toupin H and Alman R W (1956) *Amer J Med* 21 825
Felsinger von J M Lasagna L and Beecher H K (1955) *J Amer med Ass* 157 1113
Fischer H K and Dlin B M (1956) *Amer J med Sci* 232 504
French J D Verzeano M and Magoun H W (1953) *Arch Neurol Psychiat Chicago* 69 519
Fouts J R and Brodie B B (1956) *J Pharmacol* 116 480
Gero A (1954) *Science* 119 112
Graham J D P and Parker W A (1948) *Quart J Med* N S 17 153
Gravenstein J S Smith G M Sphire R D Isaacs J P and Beecher H K (1956) *New Engl J Med* 254 877

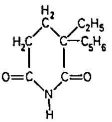
ethchlorvynol (Placidyl), resembles it in many ways, being an oily liquid absorbed from the small gut, effective in about 20 minutes with not only hypnotic but sedative anticonvulsive and muscle relaxing properties Since it is broken down in the liver and not excreted by the kidneys it may be used in kidney disease Anaesthetists are likely to use these drugs only for short periods and in these circumstances they seem relatively safe respiration being little affected even by large doses although occasionally hypersensitivity with muscular weakness and hypotension may occur Nausea excitement and rashes have also been recorded The dose range resembles that of methyl pentynol



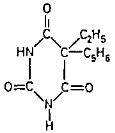
METHYLPENTYNOL



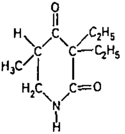
ETHCHLORVYNOL



GLUTETHIMIDE



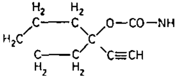
PHENOBARBITONE



METHYLPRYLONE

Glutethimide (Doriden) and methylprylone (Noludar) are rather similar members of a new group of longer acting sedative hypnotics which do not even in gross overdose depress respiration although hypotension and circulatory collapse may occur noradrenaline or other pressor amines are useful in treatment The mode of excretion is not known occasional skin rashes and hangover have been reported and there have been suggestions of possible withdrawal symptoms after prolonged administration

These four drugs which do not depress respiration so much as do the barbiturates are medium acting to long acting sedatives Ethinamate (valmidate) is a rapid and short acting sedative hypnotic overdose of which will cause



ETHINAMATE

respiratory paralysis in animals but in man 28 grammes did not cause death It is almost completely broken down in the body but since the liver and kidneys do not seem to be involved it may be useful in advanced disease of these organs

While these newer drugs can certainly be useful in special circumstances they have limitations and unwanted side effects Some are notably free from respiratory depression but their place in anaesthetic practice is not yet certain and they are perhaps best regarded as the promising forerunners of other and better drugs

Reference has been made to pharmacological work in another direction which may prove fruitful Sedatives and narcotics with which there has long been familiarity can have their action increased by a variety of new agents, some of which may act by inhibiting enzymes which are concerned in the breakdown of the drug in the brain tissue In this way drug action may be enhanced in the brain allowing smaller dosage and hence less unwanted side effects elsewhere in the body

Thus progress in anaesthesia depends largely on pharmacology Indeed, a wide knowledge of drugs has become part of the grounds upon which anaesthesiology claims recognition as a specialty but the title doctor must continue to be justified by our wisdom in their use

REFERENCES

Ballantine I D (1957) *Lancet* 1 251
Beard A J W (1954) *Proc R Soc Med* 47 407
Beckett A H and Casy A F (1954) *J Pharm Lond* 6 986
Beecher H K (1946) *Ann Surg* 123 96
— (1955) *J Amer med Ass* 159 1602
— (1956) Presentation at 17th Meeting of Committee on Drug Addiction and Narcotics National Research Council Washington D C
— (1956a) *J chron Dis* 4 11
— (1956b) *J Amer med Ass* 161 1609
— (1956c) *Amer J Med* 20 107
— Keats A S Mosteller F and Lasagna L (1953) *J Pharmacol* 109 393
Bein H S (1956) *Pharmacol Rev* 8 435
Belleville J W and Artusio J F (1955) *Anesthesiology* 16 379
Braenden O J Eddy N B and Halbach H (1955) *Bull World Hlth Org* 13 937
Brodie B B and Axelrod J (1949) *J Pharmacol* 97 58
— Shore P A Silver S L and Pulver R (1955) *Nature* 175 1133
Chapman W P (1944) *Psychosom Med* 6 252
Chen J Y P (1956) *J Pharmacol* 117 451
Cleghorn R A Graham B F Campbell R B Rublee N K Elliott F H and Saffran M (1950) In *Proc First Clin ACTH Conf* Philadelphia Blakiston
Cohen E N and Beecher H K (1951) *J Amer med Ass* 147 1664
Cullen S C and Santos C C (1954) *Arch Surg* 69 410
Dundee J W (1957) *Brit J Anaesth* 29 28
Eckenhoff J E Hoffman G L and Dripps R D (1952) *Anesthesiology* 13 242
Eddy N B Halbach H and Braenden O J (1956) *Bull Wld Hlth Org* 14 353
Fastier F N Speden R N Waal H (1957) *Brit J Pharmacol* 12 251
Fazekas J F Albert S N and Alman R W (1955) *Amer J med Sci* 230 128
— Toupin H and Alman R W (1956) *Amer J Med* 21 825
Felsinger von J M Lasagna L and Beecher H K (1955) *J Amer med Ass* 157 1113
Fischer H K and Dlin B M (1956) *Amer J med Sci* 232 504
French J D Verzeano M and Magoun H W (1953) *Arch Neurol Psychiat Chicago* 69 519
Fouts J R and Brodie B B (1956) *J Pharmacol* 116 480
Gero A (1954) *Science* 119 112
Graham J D P and Parker W A (1948) *Quart J Med* N S 17 153
Gravenstein J S Smith G M Sphire R D Isaacs J P and Beecher H K (1956) *New Engl J Med* 254 877

Grenell R G Mendelson J and McElroy W D (1955) *Arch Neurol Psychiat Chicago* **73** 347
Gross E G and Schiffrin M J (1955) *Clinical Analgesics* Baltimore Williams and Wilkins
Gruber C M Miller C L Finneran J and Chernish S M (1956) *J Pharmacol* **118** 280
Hardy J D Wolff H G and Goodell H (1940) *J clin Invest* **19** 649
Harris S C and Worley R C (1953) *Proc Soc exp Biol N Y* **83** 515
Hartley F (1956) *Pharm J* **177** 245
Heath R G (1954) *Symposium on Sedative and Analgesic Drugs* Baltimore Williams and Wilkins
Hess S M Shore P A and Brodie B B (1956) *J Pharmacol* **118** 84
Hewer A J H, Keele C A Keele K D and Nathan P W (1949) *Lancet* **1** 431
Hill H E Belleville R E and Wikler A (1955) *Arch Neurol Psychiat Chicago* **73** 602
Holmes J M (1956) *Lancet* **2** 334 765
Houde R W and Wallenstein S L (1955) *Fed Proc* **14** 353
Javert C T and Hardy J D (1951) *Anesthesiology* **12** 189
Keasling H H and Gross E G (1956) *Anesthesiology* **17** 809
Keats A S (1956) *J chron Dis* **4** 72
— and Beecher H K (1950) *J Pharmacol* **100** 1
— — (1952) *Ibid* **105** 109
— and Telford J (1956) *Ibid* **117** 190
Keele K D (1948) *Lancet* **2** 6
Keele C A (1957) Personal communication
King E E (1956) *J Pharmacol* **116** 404
Kjaer Larsen J (1956) *Lancet* **2** 967
Lasagna L and Beecher H K (1954) *J Pharmacol* **112** 356
— Mosteller F von Felsinger J M and Beecher H K (1954) *Amer J Med* **16** 770
— von Felsinger J M and Beecher H K (1955) *J Amer med Ass* **157** 1006
Leduc E H and Slaughter D (1945) *Curr Res Anesth* **24** 147
Lessin A W Parkes M W (1957) *Brit J Pharmacol* **12** 2 245
Lewis D L and Thompson W A L (1953) *Brit med J* **1** 973
Lightstone H and Nelson J W (1954) *J Amer pharm Ass (Sci Ed)* **43** 263
Locket S (1956) *Proc R Soc Med* **49** 585
Lundy J S (1956) *J Amer med Ass* **162** 97
Magoun H W (1950) *Physiol Rev* **30** 459
Nilsson E (1951) *Acta med scand* **139** Suppl 253
Papper E M Brodie B B and Rovenstine E A (1952) *Surgery* **32** 107
Paton W D M (1957) *Brit J Pharmacol* **11** 119
Payne J P (1954) *Brit J Anaesth* **26** 22
Pletscher A Shore P A and Brodie B B (1955) *Science* **122** 374
Radouco Thomas C (1957) *Anaesthesist* **6** 109
Robson J M and Keele C A (1950) *Recent Advances in Pharmacology* London Churchill
Schaumann O (1956) *Brit med J* **2** 1091
Siker E S (1956) *Brit med J* **2** 1326
Shulman A Shaw F H Cass N M and Whyte H M (1955) *Brit med J* **1** 1238
Slaughter D and Wright F T (1944) *Curr Res Anesth* **23** 115
Swerdlow M (1957) *Anaesthesia* **12** 42
Szerb J C and McCurdy D H (1956) *J Pharmacol* **118** 446
Walaszek E F and Abood L G (1956) *Science* **124** 440
White G C and Sweet W H (1943) *Pain* Baltimore Williams and Wilkins
Wikler A (1944) *J Pharmacol* **80** 176
— (1945) *Proc Soc exper Biol* **58** 193
— (1950) *Pharmacol Rev* **2** 435
Wolf S and Pinsky R H (1954) *J Amer med Ass* **155** 339

CHAPTER 5

LOCAL ANAESTHETIC DRUGS: THEIR MODE OF ACTION AND RECENT ADVANCES

J. C. GEDDES

CHEMICAL STRUCTURE OF LOCAL ANAESTHETICS

A REMARKABLY large number of molecular configurations are able to produce local anaesthesia, and this property has been attributed to drugs of many varied classes. However, numerous compounds which from their general chemical structure might be expected to possess local anaesthetic properties are in fact inactive. As shown by Buchi (1952) in a comprehensive review, the relationship between structure and function can be found only within narrow limits, and then only in a series of compounds which are practically homologous. The basic esters of benzoic acid and para-aminobenzoic acid are excellent examples. It is significant that it is to this group of compounds that the majority of the new local anaesthetics belong.

The introduction of the amino group into the aromatic ring markedly increases the anaesthetic activity. The position of the amino group is important. The para position results in greater activity than does the meta or ortho position. Alkylation of this amino group increases both potency and toxicity. When the amino group of procaine is thus modified, the methyl-amino compound is only slightly more potent, but its potency increases through the ethyl and propyl homologues to the butyl. Amethocaine (p-butyl-amino-benzoyldimethylaminoethanol) is some ten to twenty times as potent as procaine (Bonica, 1951).

Many attempts have been made to produce new local anaesthetics, and Quevauviller (1952) has traced the various modifications of the basic local anaesthetic molecule. To be successful it must have certain properties.

Lipoid solubility

Narcotics display a parallelism between their narcotic activity and their relative lipoid solubility. This observation naturally led to speculation as to whether or not a similar relationship holds for the local anaesthetics (Bryce-Smith, 1950). The narcotics are, however, electrically neutral, chemically indifferent compounds, thus differing from the ionized local anaesthetics. Following a study of a large number of local anaesthetics, Lofgren (1948) found no correlation between their blocking potencies and their partitions between lipoid and water. However, between the groups of related compounds there was a certain degree of similarity between partition coefficient and blocking potency; thus, though it was not the only important factor, it did have some bearing on the blocking effect.

Quevauviller (1952) has divided the local anaesthetic molecule into three parts

medullated or non medullated Both fibres possess a central core of semifluid axoplasm which is not covered by a histologically identifiable surface membrane There is however a functional membrane which separates the intracellular contents from the extracellular fluid In the medullated nerve there is a further insulating layer, namely the medullary sheath This consists of concentric sheets of protein interspaced between layers of lipoid material mainly lecithin

Nodes of Ranvier

The medullary sheath is interrupted at regular intervals by the nodes of Ranvier Hess and Young (1952) have recently reviewed our knowledge of these important areas Histologically there are other areas where breaks can be seen in the myelin

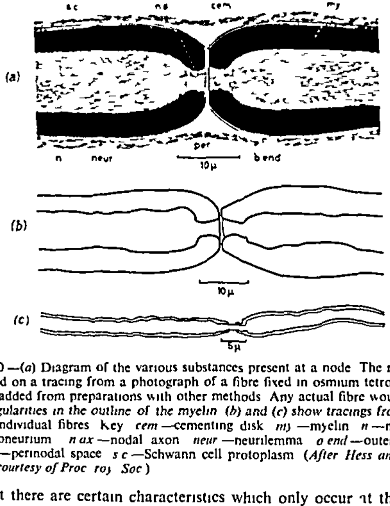


FIG 10 —(*a*) Diagram of the various substances present at a node The reconstruction is based on a tracing from a photograph of a fibre fixed in osmium tetroxide but details are added from preparations with other methods Any actual fibre would show greater *irregularities in the outline of the myelin (b) and (c) show tracings from photographs* of individual fibres Key *cem*—cementing disk *my*—myelin *n*—nucleus of outer endoneurium *n ax*—nodal axon *neur*—neurilemma *o end*—outer endoneurium *per*—perinodal space *s c*—Schwann cell protoplasm (*After Hess and Young (1952) by courtesy of Proc roy Soc*)

sheath but there are certain characteristics which only occur at the nodes (Fig 10) There is a reduction in the diameter of the axon which is restricted to the node proper At this point the myelin sheath dips inwards in a smooth rounded contour being covered with the inturning of a layer of the neurillemma As the two layers dip towards the axon they fuse and give an appearance of a cement like disk around the node The region of the axon free of myelin is less than 1 μ in length and 5 μ or more in radial thickness This disk thus forms a cuff of sclero protein separating the two ends of the myelin and it is through this that the passage of ions occurs during conduction of a nerve impulse That this is an area

(1) A hydrophilic group, usually an amino alcohol or isosteric group, which provides the necessary water solubility

(2) An intermediate portion in the form of an ester or isosteric group which he considers as the pivot

(3) A lipophilic portion consisting of cyclic and heterocyclic hydrocarbon formations including a varying number of substituted isosteric groups This portion provides the lipoid solubility required for local anaesthetic activity

It is however, essential that these hydrophilic and lipophilic properties are balanced for if the former predominates sufficient active free base will not be available following injection If on the other hand the molecule is too lipophilic it cannot be dissolved in water and thus becomes clinically useless

Quaternary ammonium compounds

Nador and his colleagues (1953) described a series of quaternary ammonium compounds possessing local anaesthetic activity Onset of anaesthesia was however slow Recently choline 2 6 xylyl ether bromide, also a quaternary compound has been demonstrated to possess local anaesthetic activity (Hey and Willey 1954) and onset of action was rapid These quaternary compounds do not have any activity as topical anaesthetics while the tertiary homologues have been shown to be effective This is in accord with the general conclusion that the tertiary amino group is concerned with the penetration of membranes

Ionization in solution

Local anaesthetics are the salts of weak bases and as such dissociate in aqueous solution The degree of dissociation depends upon the ionization constant of the local anaesthetic and the *p*H of the solution Many workers have demonstrated that it is the free base which is the active ion (Trevan and Boock 1927 Ehrenberg 1948 Skou 1954) At an alkaline *p*H there is more free base available and, when testing for local anaesthetic activity on isolated nerve or by topical application to the cornea, it can readily be demonstrated that as the *p*H approaches 7 4 increased activity is present It was because of this observation that buffered solutions were introduced but unfortunately little is to be gained when they are used for infiltration for the tissues possess considerable buffering powers and can readily adjust injected solutions to the *p*H of the body In clinical practice therefore as found by Tainter (1941) no advantage was observed as regards the speed of onset of anaesthesia following the use of buffered solutions It should however be noted that solutions of too low *p*H can cause tissue damage and severe necrosis has resulted from procaine at a *p*H of 1 0–2 9 (Kendall 1948)

TRANSMISSION OF A NERVE IMPULSE

It is relevant to consider briefly some of the advances in our knowledge of the transmission of a nerve impulse These have recently been summarized in excellent reviews by Toman (1952) and Muralt (1954)

The structure of nerves

The unit of nervous tissue consists of the nerve cell and its processes the dendrites and the axon or axis cylinder The axon is dependent upon an intact connexion with the nerve cell for nutrition and survival Nerve fibres may be either

of great permeability is demonstrated by the fact that when dyes are applied to medullated nerves it is only at the nodes that they enter and diffuse along the fibres Methylene blue stains the whole of this area and by its use it has been possible to demonstrate that nodes are not confined to peripheral nerves but are also present in the medullated nerves in the central nervous system

Tasaki (1953) has shown that in a medullated nerve the node is the only place at which it can be excited The part that the nodes play in saltatory conduction in nerve has been reviewed by Stampfli (1954) Their presence permits an extremely efficient conduction of an impulse with the expenditure of considerably less energy than would have otherwise been necessary (Hodgkin, 1951)

Metabolism of nerves

The excitation and polarization of nerves necessitates a supply of energy During conduction of an impulse oxygen is consumed carbon dioxide produced and heat evolved There is however no fixed relationship between this rate of oxygen uptake and the capacity for nerve tissue function (Brink, Bronk and Larrabee 1946)

Sherif (1930) has demonstrated that procaine and cocaine inhibit the respiration of the sciatic nerve of the rabbit It was thus suggested that local anaesthetics act by inhibiting the utilization of oxygen Experiments by Watts (1949) in which brain homogenates and varying substrates were used showed that a correlation existed between the relative ability of the local anaesthetics to inhibit the intra cellular oxidation of glucose succinate and ascorbate, and their potencies as local anaesthetics Ryman and Walsh (1954) found that cocaine suppresses respiration and aerobic acetylcholine synthesis in the brain In their study they were able to show that the entry of active acetate in the citric acid cycle was being blocked by the local anaesthetics It was also shown in a further paper (Ryman and Walsh 1955), that the synthetic local anaesthetics exerted a similar effect

It is however known that the local anaesthetics may block conduction in nerves at concentrations which cause no decrease in the uptake of oxygen (Larrabee Posternak and Bronk 1947) Furthermore decreased oxygen con sumption has been demonstrated to occur following the application of sodium azide yohimbine and hydroxalamine to a nerve fibre without impairment of conduction (Doty and Gerard 1950)

When potassium chloride is applied to a nerve it causes depolarization and also a considerable increase in the oxygen consumption Experiments with rats brain cortex slices (Geddes and Quastel 1956) have shown that local anaesthetics are able to inhibit this potassium effect on respiration Further, they do so at con centrations which in the absence of extra potassium exert little depression on respiration The potencies of the various local anaesthetics as inhibitors of potassium accelerated respiration have been shown to parallel their anaesthetic activities It is suggested that the local anaesthetics influence the passage of ions in nerves and it may be due to this cause that a secondary effect on oxygen consumption is observed It is concluded that the local anaesthetics do not block conduction by directly interfering with aerobic metabolism of nerves

Possible relation to the transmittor substance

It has been suggested that acetylcholine or perhaps some other humoral trans mittor plays a role in nervous conduction (Wilson and Nachmansohn 1954) It

has been presumed that acetylcholine is stored in an inactive bound form and that stimulation of the nerve releases the ester which combines with a receptor protein It is this reaction which it is claimed produces the complex changes in the ion permeability of the cell membrane associated with the action potential The hydrolysis of the acetylcholine by cholinesterase removes it from the acetylcholine receptor and allows the nerve to return to its resting condition

It is well known that the local anaesthetics are potent inhibitors of the acetyl choline serum cholinesterase system (Hazard Corteggiani and Pelou 1944) This inhibition is not however specifically associated with the interruption of conduction for many substances such as the vegetable dyes and morphine are inhibitors of serum cholinesterase yet have no direct effect as local anaesthetics

MODIFICATION OF THE MECHANISM OF CONDUCTION BY LOCAL ANAESTHETICS

The ionic hypothesis of impulse conduction is well reviewed by Eccles (1953) Local anaesthetics block conduction without appreciably altering the resting state of polarized nerves (Bennett and Chinburg 1946) It is not known how the local anaesthetics stabilize the plasma membrane but Shanes (1948) has suggested that they appear to reduce the membrane permeability to potassium The rate of transport of potassium from the inside to the outside of the fibre is a controlling factor during stimulation Further experiments by Straub (1956) demonstrate a definite effect of procaine on the permeability of the nodal membrane to potassium ions and also to the transport of sodium In myelinated nerves the ionic migration only occurs at the nodes of Ranvier since the myelin sheath acts as a very efficient barrier or insulator (Lussier and Rushton 1952)

As would be expected local anaesthetics exert their effect only at the nodes of Ranvier being ineffective in the internodal region (Kato 1936 Tasaki 1939)

This stabilization of the plasma membrane with maintenance of the demarcation potential is in direct contrast to the effect of potassium or calcium These ions have been shown to cause a block by depolarizing the resting fibre (Bennett and Chinburg 1946) thus removing the normal demarcation potential and making impossible the changes in polarity associated with conduction of the impulse

RECENT RESEARCH ON GENERALIZED EFFECTS OF LOCAL ANAESTHETICS

Recent researches with local anaesthetic agents have been influenced by the advances in other fields such as neurophysiology Studies by French Verzeano and Magoun (1953) with general anaesthetics and their influence on the reticular activating system have been followed by similar work on the neuropharmacology of procaine (Peterson 1955 a and b)

Intravenous administration of local anaesthetics

In 1943 Gordon first reported the injection of procaine intravenously to obtain analgesia and so achieve the painless dressing of burns After six years Mushin and Rendell Baker (1949) reviewed the numerous clinical applications for the administration of intravenous procaine It had been postulated by Graubard and Peterson (1949) that procaine so injected acted as an analgesic by being

concentrated in areas of changed permeability caused by tissue trauma The recent study by Peterson (1955a) of the neuropharmacology of intravenously administered procaine showed that the clinical procaine unit of 4 milligrams per kilogram produced no significant alterations in peripheral neurones or in transmission at preganglionic autonomic synapses At higher concentrations blocking effect was obtained on the effector side of the reflex arc where cholinergic mechanisms operate On reaching 10 milligrams per kilogram of procaine a cardiac vagal block was observed and at this dosage level myoneural block was also noted At the level of the spinal cord a graded depression of activity in the monosynaptic and multineuronal units was produced and this resulted in a general tranquillizing effect This was observed following doses as low as 3–5 milligrams per kilogram of procaine

Procaine was shown to exert a selective depressant action on the inhibitory descending influences from the brain stem reticular formation without a corresponding effect on the descending facilitatory paths which influence the motor neurone This may be the mechanism of action of the convulsant properties of local anaesthetics Toman and Davis (1949) have suggested that a threshold raising drug may by selective depression of inhibitory systems give rise to convulsions

From these experiments it is obvious that two separate effects are evident following intravenous administration and depending upon the dose given At a low concentration an initial depression of activity is observed which by a release phenomenon, can result in convulsions at a higher dosage There has recently been developed a fascinating application of these observations in which local anaesthetics have been injected intravenously to treat status epilepticus

Local anaesthetics and epilepsy

Bernhard and Bohm (1954) have recently advocated the use of intravenous lignocaine as a useful agent in the treatment of status epilepticus It has been demonstrated that, in cats and monkeys, intravenous administration of local anaesthetics such as procaine butethamine, lignocaine diethoxin and amethocaine reduces the cortical after discharge following repetitive cortical stimulation of exposed brain (Bernhard and Bohm, 1955) The efficiency of these drugs parallels their anaesthetic potency Amethocaine was the most efficient but owing to its toxicity it was not recommended for clinical use The concurrent administration of pentobarbitone in a dose which did not affect the cortical after discharge potentiated the effects of lignocaine

Bernhard Bohm and Hojeberg (1955) reported the use of lignocaine administered in an intravenous drip to treat cases of status epilepticus Some patients responded favourably to 2 milligrams of lignocaine per kilogram per hour but in severe status epilepticus this required to be supplemented by additional intravenous doses As in animal experiments a synergistic action of a barbiturate and lignocaine were observed This was of particular value in severe cases in which fits and spasms were controlled without a dangerously deep level of sedation

Depression of laryngeal reflexes

Lignocaine has been administered intravenously in association with general anaesthesia in 75 patients to depress pharyngeal and laryngeal reflexes No unto

ward reactions were observed in electrocardiograms, electroencephalograms and blood pressure tracings (Steinhause and Howland 1957). It is claimed that the depression of these reflexes with intravenous lignocaine permitted very light planes of anaesthesia to be maintained during otolaryngological operations.

ATTEMPTS TO ACHIEVE PROLONGED ANAESTHESIA

In an effort to control post operative pain many attempts have been made to develop an anaesthetic solution with a prolonged duration of action.

Oily solutions

For use following proctological surgery the bases of local anaesthetics were dissolved in oily solutions usually benzyl alcohol and butyl p aminobenzoate, on the assumption that the base would be slowly liberated from the oil and thus a prolonged effect result. It was however demonstrated (Kelly, 1947) that the effect of the local anaesthetic could wear off in a few hours. Duncan and Jarvis (1943) showed that any prolonged effect observed was in fact due to the degenerative effect of benzyl alcohol on the nerves. The duration of anaesthesia was thus dependent upon regenerative repair and not on the pharmacological release of the local anaesthetic. Further it was found that unless 10 per cent benzyl alcohol was present the nerves were not damaged and this was said to account for the reported failures to achieve a prolonged effect with some of the solutions which contained only 5 per cent benzyl alcohol.

The presence of the oil was also shown to lead to an inflammatory reaction and to cause suppuration and even necrosis. It was felt that if some other way could be found of dissolving the anaesthetic bases prolonged anaesthesia might still be achieved following their liberation over a period of time. Meidinger (1945) thought of adding 40 per cent polyvinylpyrrolidone to increase the viscosity of the solution and achieved a certain prolongation of action but not sufficient to be of value clinically.

Non-oily solutions

In an attempt to dispense with the oily solution Efocaine was developed. It consisted of procaine procaine base and 5 per cent butyl p aminobenzoate dissolved in 2 per cent polyethylene glycol (300) and 78 per cent propylene glycol (Ansbro and his co workers 1952).

These concentrations were chosen following a study of the solubility of the anaesthetic bases in propylene glycol. It was found that there was an instability of procaine in solution but if a small amount of polyethylene glycol was added it acted as a protective polymer. The procaine base and butyl p aminobenzoate were dissolved to their saturation limits so that, following the addition of even minimal quantities of tissue fluids, precipitation of the active bases occurred; these then would be a depot of the precipitated bases. Anaesthesia could be produced it was claimed, for from 12–14 days and no permanent damage resulted. Weinberg (1952) in animal experiments noted following injection of this solution some fibrous reaction about nerve trunks and that the muscles showed some evidence of necrosis in the line of the injection. In animals examined at autopsy between 89 and 98 days after injection, sections of nerve showed no evidence of

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The presence of the oil was also shown to lead to an inflammatory reaction and to cause suppuration and even necrosis It was felt that if some other way could be found of dissolving the anaesthetic bases prolonged anaesthesia might still be achieved following their liberation over a period of time Meidinger (1945) thought of adding 40 per cent polyvinylpyrrolidone to increase the viscosity of the solution and achieved a certain prolongation of action but not sufficient to be of value clinically

Non-oily solutions

In an attempt to dispense with the oily solution Efocaine was developed It consisted of procaine procaine base and 5 per cent butyl p aminobenzoate dissolved in 2 per cent polyethylene glycol (300) and 78 per cent propylene glycol (Ansbro and his co workers 1952)

These concentrations were chosen following a study of the solubility of the anaesthetic bases in propylene glycol It was found that there was an instability of procaine in solution but if a small amount of polyethylene glycol was added it acted as a *protective* polymer The procaine base and butyl p aminobenzoate were dissolved to their saturation limits so that, following the addition of even minimal quantities of tissue fluids precipitation of the active bases occurred these then would be *a depot* of the precipitated bases Anaesthesia could be produced it was claimed, for from 12–14 days and no permanent damage resulted Weinberg (1952) in animal experiments noted following injection of this solution some fibrous reaction about nerve trunks and that the muscles showed some evidence of necrosis in the *line of the* injection In animals examined at autopsy between 89 and 98 days after injection sections of nerve showed no evidence of

concentrated in areas of changed permeability caused by tissue trauma The recent study by Peterson (1955a) of the neuropharmacology of intravenously administered procaine showed that the clinical procaine unit' of 4 milligrams per kilogram produced no significant alterations in peripheral neurones or in transmission at preganglionic autonomic synapses At higher concentrations blocking effect was obtained on the effector side of the reflex arc, where cholinergic mechanisms operate On reaching 10 milligrams per kilogram of procaine a cardiac vagal block was observed and at this dosage level myoneural block was also noted At the level of the spinal cord a graded depression of activity in the monosynaptic and multineuronal units was produced and this resulted in a general tranquillizing effect This was observed following doses as low as 3-5 milligrams per kilogram of procaine

Procaine was shown to exert a selective depressant action on the inhibitory descending influences from the brain stem reticular formation without a corresponding effect on the descending facilitatory paths which influence the motor neurone This may be the mechanism of action of the convulsant properties of local anaesthetics Toman and Davis (1949) have suggested that a threshold raising drug may, by selective depression of inhibitory systems give rise to convulsions

From these experiments it is obvious that two separate effects are evident following intravenous administration and depending upon the dose given At a low concentration an initial depression of activity is observed which by a release phenomenon, can result in convulsions at a higher dosage There has recently been developed a fascinating application of these observations in which local anaesthetics have been injected intravenously to treat status epilepticus

Local anaesthetics and epilepsy

Bernhard and Bohm (1954) have recently advocated the use of intravenous lignocaine as a useful agent in the treatment of status epilepticus It has been demonstrated that in cats and monkeys intravenous administration of local anaesthetics such as procaine butethamine lignocaine diethoxin and amethocaine reduces the cortical after discharge following repetitive cortical stimulation of exposed brain (Bernhard and Bohm 1955) The efficiency of these drugs parallels their anaesthetic potency Amethocaine was the most efficient but owing to its toxicity it was not recommended for clinical use The concurrent administration of pentobarbitone in a dose which did not affect the cortical after discharge potentiated the effects of lignocaine

Bernhard Bohm and Hojeberg (1955) reported the use of lignocaine administered in an intravenous drip to treat cases of status epilepticus Some patients responded favourably to 2 milligrams of lignocaine per kilogram per hour but in severe status epilepticus this required to be supplemented by additional intravenous doses As in animal experiments a synergistic action of a barbiturate and lignocaine were observed This was of particular value in severe cases in which fits and spasms were controlled without a dangerously deep level of sedation

Depression of laryngeal reflexes

Lignocaine has been administered intravenously in association with general anaesthesia in 75 patients to depress pharyngeal and laryngeal reflexes No unto

peridural anaesthesia as the dural sac was continuously perfused to get sufficient fluid for analysis

Frumin and his colleagues (1953) described a method of inserting a catheter to the level of the twelfth thoracic or first lumbar vertebra in humans. A further catheter was inserted intrathecally at the third or fourth lumbar interspace and in most of the experiments advanced to a point opposite to the extradural catheter. Segmental anaesthesia followed peridural injection of 20 millilitres of 2 per cent procaine; a threshold concentration of 0.2 milligrams per millilitre for spinal blocks as found by Helrich and his co-workers (1950) was aspirated by the subdural catheter. Following wearing-off of sensory spinal block, the concentrations of the procaine in the spinal fluid samples were appreciably reduced. It is concluded that some at least of the anaesthesia is attributable to penetration of the dura. Frumin and his associates (1954), by injecting the threshold dose of procaine in humans, suggested that the spinal ganglia were the most sensitive structures for chemical interception of sensory pathways. Following autoradiographic study, Howarth (1949) could find no evidence of penetrance of radioactive dibromo procaine to the spinal marrow.

Saker and Shroder (1954) were not convinced by this and claim that the point of attack is external to the dura. They said that the high cerebrospinal fluid concentrations were due to a puncture hole drainage or to dural injury in the field of the peridural anaesthesia. Further, when the pressure of the cerebrospinal fluid was increased, there was no penetration of peridural deposited local anaesthetic in the lumbar region, whereas when the pressure in the cerebrospinal fluid was decreased a high concentration could be rapidly achieved in the cerebrospinal fluid.

Frey (1954) was able to demonstrate traces of procaine in cerebrospinal fluid from the suboccipital region of dogs following lumbosacral peridural anaesthesia combined with postural elevation of the legs. These experimental observations may be of value in interpreting untoward reactions following peridural anaesthesia.

It is obvious however that the full implication of the distribution of large volumes of local anaesthetic deposited into the peridural space is not to be ignored. Batson's (1940) study of the vertebral venous system is also relevant. These veins may contain up to 200 millilitres of blood and, being devoid of valves, allow direct access to the venous system of the brain. The flow of blood in the vertebral veins is of considerable interest, for if the intra-abdominal pressure is raised there is obstruction to the portal system and the blood from the lower limbs and pelvis flows mainly upwards *via* the vertebral veins. The rapid absorption of peridural injections which may follow when adrenaline is omitted from the solutions can give rise to a relatively high incidence of reactions to peridural anaesthesia (Ansbro and his colleagues 1954).

Soehring and his co-workers (1954) demonstrated that if repeated extradural injections of a high molecular allyl polyethylene oxide are made, anatomical changes in the intradural portions of the nerve roots occur which can be explained only by the passage of the anaesthetic from the peridural space into the cerebrospinal fluid.

It would appear on balance that the dura is permeable to local anaesthetics and some if not all the effect of peridural injection is due to there being an effective concentration within the cerebrospinal fluid.

inflammatory reaction and no perineural fibrosis The nerve fibres showed focal loss of myelin in their sheaths as was evidenced by the presence of scattered vacuoles It was concluded that no significant permanent damage resulted to the tissues involved and that Efocaine did not cause a foreign body giant cell reaction

In the use of Efocaine it was recommended that only minimal quantities of the solution be injected at one site and aspiration should be carried out before and frequently during the injection Intravenous injection was contra indicated Clinical reports of the successful use of Efocaine appeared (Roualle, 1952)

Pain was however, reported on injection and it was suggested that this was due to the presence of highly hypertonic solvents It was recommended that superficial injection should be avoided However, pain in the distribution of injected nerves was also reported by Bartlett and Eastwood (1953) Following post operative paravertebral injection of the recommended dose serious neurological complications were reported by Shapiro and Norman (1953) In one patient transverse *myelitis with hemiplegia developed and the remaining patients had symptoms* of toxic neuritis and prolonged sympathetic block Death has followed the injection of 1 5 millilitre of Efocaine in the eighth intercostal space well away from the spine (Angerer, Su and Head, 1953) The patient suddenly complained of a severe knife like ' pain in his back and radiating down both legs which were completely paralysed for several minutes Death followed 3 days later At post mortem examination extensive necrosis and acute inflammation of the spinal cord was present, and the intercostal vein was found to be thrombosed

Further investigation of the effect of Efocaine on tissues (Maykut and Ryan, *1953 Mannheimer, Pizzolato and Adriani 1954)* revealed that the adverse effect produced upon nerves was due to the solvent propylene glycol

Benzocaine and urethane solution

A recent paper (Kohn Rutter and Vitali, 1954) described an easily prepared solution of benzocaine 2 per cent and urethane 40 per cent in distilled water as safe and free from undesirable side effects This is said to work on the depot principle and the authors claim to have demonstrated this by both *in vitro* and *in vivo* experiments The solution causes pain on injection and it is suggested that either an earlier injection of procaine should be given or the injections made whilst the patient is under general anaesthesia Following the injection of the intercostal nerves it is claimed that analgesia is produced but the motor nerves are not affected This solution is also recommended for the treatment of the pain associated with amputation neuroma Concerning intravenous injection toxicity tests in mice showed that a dose about 100 times the therapeutic dose in man resulted in death It would thus appear that this particular solution may be safer and have some advantages over the proprietary preparations so far developed

RECENT INVESTIGATIONS INTO THE SITE OF ACTION OF PERIDURAL ANAESTHESIA

There are many reports of local anaesthetics being found in the cerebrospinal fluid following peridural injection including those by Numans and Havinga (1943) in calves Frey (1954) in dogs and Rudin Fremont Smith and Beecher (1951) also in dogs These experiments were radically different from clinical

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or doughy swellings sometimes persisted for periods up to three to five days (Lundquist and his colleagues 1948) Following chemical biological and clinical tests it was found that acid solutions of lignocaine and procaine liberated in certain circumstances traces of copper, nickel and zinc from hypodermic syringes made entirely or partly from metal Copper was the most toxic ion After further experiments Weidling (1948) demonstrated that adrenaline was essential to the local toxic action of these ions by preventing their absorption from the site of injection It is possible that similar reactions have in the past been confused with allergic manifestations

Adler, Kesztyus and Simon (1950) have investigated the importance of specificity in allergy to local anaesthetics by examining the precipitin reactions of sensitized rabbits to 25 different local anaesthetics using procaine azo protein as an antigen The esterified derivatives of p aminobenzoic acid in which the amino group had no side chain gave a positive precipitin reaction thus demonstrating that strong group specificity was present The significance of this is that when allergy exists to one anaesthetic of the procaine series local anaesthetics of different chemical structure and not derived from p aminobenzoic acid can be safely used Claims for Unacaine in which the meta position of the amino group on the benzene ring was thought to decrease the likelihood of the occurrence of allergy, have not been completely fulfilled for Kalman (1954) has described a case of angioneurotic oedema with a positive skin test for Unacaine

Lignocaine being a derivative of an anilide differs chemically from local anaesthetics such as procaine monocaine amethocaine and 2 chloroprocaine and has been recommended as a substitute when the patient is known to be sensitive to derivatives of p aminobenzoic acid (Rickles 1953)

PROBLEMS ASSOCIATED WITH THE INTRODUCTION OF NEW COMPOUNDS

The introduction of a new local anaesthetic is justified only if it possesses properties superior to those of the drugs already in current use Countless compounds with local anaesthetic activity have been synthesized and it is fortunate that the journey from the organic laboratory to the clinic is a long one (Dornette 1954) Pharmacologists have developed many tests to compare local anaesthetic activity and these have been reviewed recently by the writer (Geddes, 1955) There is no standardization of these tests and as Lofgren (1948) points out, some authors investigate the minimal effective concentration others the duration and others again the latency time thus the situation becomes confused Many tests are difficult to perform and often are successful only in the hands of their inventor Considerable training and experience is often required before reliable information can be collected Two drugs cannot be accurately compared unless they have been tested by the same technique and the same worker and the data from different laboratories cannot be correlated

A somewhat similar comparison exists in the field of toxicity tests where considerable variation occurs owing to species differences Though an indication of toxicity can be obtained from animal experiments it is not always directly applicable to man In fact some drugs which were abandoned because of their high toxicity in animals might have been found safe if tested on man This problem

SPREADING" AGENTS

Hyaluronidase

The enzyme hyaluronidase depolymerizes hyaluronic acid and related substances producing liquefaction of viscous polysaccharide which is the cement substance of the tissue Provided that there is an adequate head of pressure behind the injected substance, the addition of hyaluronidase to local anaesthetic solutions will produce a more rapid spread of the solution through the tissues It has been added to these solutions with the aim of increasing the number of successful blocks, as well as to hasten the onset of anaesthesia However, it does not facilitate the penetration of fascial planes and its use will not always achieve the hoped for results (Eckenhoff and Kirby, 1951) It is not, as Moore (1951) has pointed out, a substitute for the correct anatomical deposition of solutions The onset of anaesthesia however, is effectively accelerated in both local infiltrations (Moore 1951) and topical anaesthesia (Howland and Papper 1951) The resulting wide spread dispersion of the local anaesthetic solution must increase the rate of absorption into the circulation and when doses which are on the borderline of toxicity are used toxic reactions are likely It has been shown that the addition of adrenaline does not inhibit the spreading properties of hyaluronidase but it does however decrease the vascularity of the area reduce the rapidity of absorption and prolong the duration of anaesthesia

Synthetic wetting agents

Triton A20 an alkylaryl polyether alcohol, is a synthetic wetting agent and has been used in dentistry to achieve a result similar to that with hyaluronidase It aids dispersion by its ability to lower surface and interfascial tensions (Tanz, Jaworski and Elkins 1951)

DERMATITIS AND LOCAL ANAESTHETICS

Localized or generalized dermatitis can ensue following sensitization to local anaesthetic drugs In 1947 the Council on therapeutics of the American Dental Association compiled a list of about 400 dentists sensitive to local anaesthetics (Council Reports 1949) A typical distribution of the lesions associated with the use of the first three fingers of the left hand as a retractor whilst injecting local anaesthetics has been described (Laden and Wallace 1949) Local anaesthetics derived from p aminobenzoic acid allied to procaine are the principal offenders Recently Gaul (1955) reported two cases in which cross sensitization occurred from p aminobenzoate in sunburn preventatives

A further source of sensitization is the current vogue of incorporating local anaesthetics in preparations used for the relief of pruritus Lane and Luikart (1951), in a comprehensive review of the literature found that of 107 cases 73 per cent had positive patch tests The authors concluded that it would seem unwise to dispense or prescribe a local anaesthetic preparation for topical use without being alert for the occurrence of epidermal hypersensitivity This possibility must not be ignored when applying liberal quantities of local anaesthetic lubricant to endotracheal tubes

Following injection of local anaesthetic solutions in certain dental clinics soft

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is not however, confined to the field of local anaesthetics, and pharmacologists are well aware of these deficiencies of animal work (Brodie 1956)

It is perhaps unfortunate that the final decision as to the suitability of a new drug can be made only following extensive clinical use Before the general release of a new local anaesthetic it should be used by competent investigators able to carry out an unbiased comparison In the past new drugs have been distributed to clinicians who have had little or no training in clinical research, and the literature is full of papers lauding new compounds where the success of the trial was based more on the number of patients than on a critical analysis of the data To enable a comparison to be made it has been suggested by Bonica (1957) that procaine be included as the standard for infiltration and block anaesthesia, and cocaine for topical application

Mumford and Geddes (1955) have discussed some of the essentials to be considered when planning a clinical investigation of a local anaesthetic

It is with these criticisms of testing methods in mind that we must analyse the data presented in the following summary of the newer local anaesthetics

NEWER LOCAL ANAESTHETICS USED CLINICALLY

The aim of research in the development of new local anaesthetics is primarily directed to producing a fully effective drug with no toxic side reactions either by local tissue damage or on systemic absorption

Following its introduction into clinical anaesthesia by Einhorn procaine has been for over fifty years the nearest approach to the ideal anaesthetic Its safety is dependent upon the speed of its destruction by the body in both plasma (Kalow 1952) and the liver (White, Dearborn and Swiss, 1955)

Unfortunately the anaesthetic property of procaine used in safe concentrations leaves much to be desired The duration of anaesthesia can be prolonged by the addition of adrenaline, but repeated injections may be required in prolonged surgery

Many attempts have been made to discover a superior local anaesthetic related to procaine The literature is full of references to derivatives of benzoic p amino benzoic and p oxybenzoic acids Carney (1951) has recently surveyed some 1 060 such compounds Among these have been some that have been given clinical trials and it is proposed briefly to summarize recent trends in this field

Substitution in side chain of procaine

2 alkoxy analogues of procaine

Luduena and Hoppe (1952) found certain consistent relationships followed an increase in the length of the 2 alkoxy side chain of the 4 aminobenzoate structure Anaesthetic activity and toxicity increased progressively with the length of the ether side chain up to the 2 butoxy analogue Activity, however increased to a greater degree than local irritancy as measured by the trypan blue test

Hydroxyprocaine (diethylaminoethyl 4 amino salicylate hydrochloride) has been used for some years in Germany (Schoog 1951 Höller, 1952)

Despite original claims that it was superior to procaine pharmacologically and clinically it was not found by the writer to possess any obvious advantages (Geddes 1956)

Propoxycaine (*Ravocaine*) (diethylaminoethyl 2 propoxy 4 aminobenzoate hydrochloride)

The propoxy derivative has been investigated by Luduena and Hoppe (1952) and found to be 8 to 9 times more active than procaine, but only twice as irritating

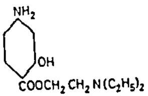
In clinical trial, an initial concentration of 0·1–0·2 per cent proved too low however Crawford (1953) found 0·5 per cent to be a satisfactory concentration in peridural anaesthesia

Tainter Wessinger and Lee (1955) describe the use of a solution of procaine 2 per cent containing 0·4 per cent propoxycaine and 1 noradrenaline 1 30 000 as being ideal for dental anaesthesia

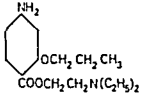
Butoxycaine (*Stmpocaine*) (diethylaminoethyl 2 butoxy-4 aminobenzoate)

The butoxy derivative was found to be 20 times as active as procaine in spinal anaesthesia while being approximately 15 times as toxic as procaine on intravenous injection in mice (Luduena and Hoppe 1952)

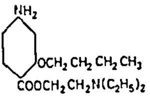
Sadove, Levin and Rose (1954) have presented a preliminary study of its efficiency as a spinal anaesthetic A concentration of 0·5 per cent in 3·75 per cent inositol proved to be easily handled The drug was found to be safe, potent and non toxic The duration of anaesthesia was between 2½ and 3 hours, depending upon whether adrenaline was present or absent



HYDROXYPROCAINE



PROPOXYCAINE



BUTOXYCAINE

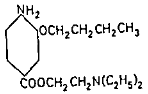
Benoxinate (*Dorsacaine*) (diethylaminoethyl 3 butoxy-4 aminobenzoate hydrochloride)

The 3 butoxy substituted compound has been investigated and in experimental animals benoxinate has about the same toxicity as cocaine It has been used as a topical anaesthetic for the cornea where it is claimed to produce less irritation yet a more intense degree of anaesthesia than comparable concentrations of amethocaine (Linn and Vey 1955) Onset of anaesthesia is rapid following instillation of a 0·4 per cent solution and this is attributed to a rapid concentration of benoxinate in the corneal epithelium (Schlegel and Swan 1954) Clinically no signs of local or systemic hypersensitivity have been observed (New and Non official Remedies 1955)

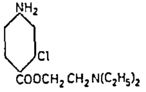
Halogen substitution

Foldes Davis and Plekss (1956) have investigated the effect of halogen substituted benzoic acid derivatives Of these 2 chloroprocaine (Nesacaine) (diethylaminoethyl 2 chloro 4 aminobenzoate hydrochloride) has been shown to be hydrolysed *in vitro* 4 times as fast as procaine with human sera (Aven and Foldes 1951) An aqueous solution is stable for several months but it has been observed that the hydrolysis in alkaline solution is accelerated when compared to procaine In toxicity tests in mice 2 chloroprocaine has approximately half the toxicity of procaine, while the duration of anaesthesia was greater when measured

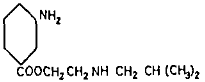
by the intradermal weal test 2 chloroprocaine has been successfully used clinically and it is claimed to be extremely safe owing to its high rate of hydrolysis In epidural anaesthesia the use of a shorter acting agent such as 2 chloroprocaine gives greater controllability to the continuous technique (Foldes Davis and Plekss 1956) A 3 per cent solution with adrenaline is recommended for caudal and epidural blocks



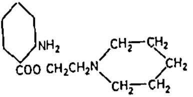
BENOXINATE



CHLOROPROCAINE



UNACAINE



PIRIDOCAINE

Meta amino compound

Unacaine (isobutylaminoethyl 3 aminobenzoate hydrochloride)

In mice Unacaine has approximately one third the toxicity of procaine When administered subcutaneously the anaesthetic activity is claimed to be at least double that of procaine

Nevin Epstein and Nevin (1952) reported its use in clinical dentistry where anaesthesia was claimed to be of rapid onset with a low incidence of toxic symptoms

Piperidine derivative

Piridocaine (Lucaine) (B (2 piperidylethyl 2 aminobenzoate hydrochloride)

Finer and Rovenstine (1947) first used piridocaine clinically for spinal anaesthesia and observed that there was a selective action on sensory and autonomic nervous tissue Patients were described as being able to move their legs with no evidence of paralysis of intercostal muscles during surgical procedures without pain and with no complaints about relaxation from the surgeon

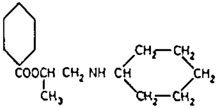
Conner and Dripps (1950) observed some diminution of motor power in the lower extremity in every case but in the majority it was barely perceptible or minimal This selective anaesthesia was thought to be a function of concentration and dosage By increasing the percentage from 1 to 2 per cent and increasing the dose from 20 to 60 milligrams motor paralysis could be demonstrated Recently the position of piridocaine in spinal anaesthesia has been critically reviewed by Greene and his colleagues (1956) following the experience of 6 000 spinal blocks These authors claim that piridocaine offers many advantages over other agents where it is desirable to retain motor power as for example during labour

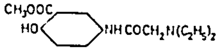
Derivatives of benzoic acid

Cyclaine (Hexylcaine) (1 cyclohexylamino 2 propyl benzoate hydrochloride) was first synthesized by Hancock and Cope (1944) It has a toxicity slightly

greater than procaine Orkin and Rovenstine (1952) presented a preliminary report of its use in regional and topical anaesthesia Ansbro and his colleagues (1954) in a series of lumbar epidural anaesthetics compared lignocaine with it A 1 per cent solution of cyclaine did not give the desired relaxation for abdominal surgery but with a 2 per cent concentration it fulfilled all the requirements of epidural anaesthesia

Anderson and Ruben (1952) found that burning on initial injection with some residual soreness occurred in some patients when cyclaine was used for nerve


CYCLAINE

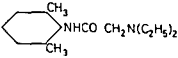

NIRVANINE

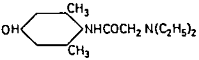
block This property was also commented on by other workers but was claimed not to be a real inconvenience to the patient

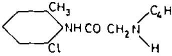
Clarke Orkin and Rovenstine (1954) using an objective method of testing for topical anaesthesia found that 2 5 per cent cyclaine is an adequate concentration for brief anaesthesia but for a longer duration 5 per cent is advisable

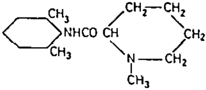
Derivatives of xylidine

Nirvanine is of historical interest for it was investigated by Einhorn and Oppenheimer (1900) before the discovery of procaine Though nirvanine possesses a low toxicity it was found to be strongly irritating to tissues and thus was not recommended for clinical use No further related compounds were described for use as local anaesthetics till the introduction of lignocaine


LIGNOCAINE


HYDROXYLIGNOCAINE


HOSTACAINE


CARBOCAINE

Lignocaine Lidocaine N N R (*Xylocaine*) (Diethylaminoacet 2 6 xylidide hydrochloride) Lignocaine was synthesized in 1946 by Lofgren who in 1948 published a monograph on his studies (Lofgren 1948) The toxicity compares favourably with procaine but is greater at concentrations above 1 per cent (Goldberg 1949)

Lignocaine is extremely stable in solution (Bullock and Grundy 1955) and as it is not an ester it is unaffected by pseudocholinesterase (procainesterase) Recent work however has demonstrated that liver slices can hydrolyse *in vitro* the amide linkage (Geddes and Douglas 1956)

A comprehensive survey of the clinical literature by Weidling (1952) and a review by Southworth and Dabbs (1953) of over 68,000 cases indicate that lignocaine is the nearest approach to the ideal local anaesthetic since the introduction of procaine

Hydroxylignocaine Pharmacological investigations by Krantz, Lu and O Malley (1954) demonstrated that hydroxylignocaine possessed a lower toxicity than did lignocaine, but at the same time the duration of anaesthesia was also considerably diminished

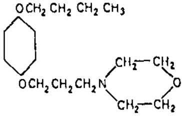
Hostacaine (Butylaminoacet 2 chloro 6 toluidide hydrochloride) Ther (1953) found hostacaine to be twice as toxic as procaine on rapid intravenous injection He was also able to demonstrate cleavage of the amide linkage which takes place mainly in the liver Local anaesthesia is prompt in onset and the effect lasts longer than with procaine Thorban (1956) has summarized references to its use in Germany He reports its successful use in over 500 major operations

Carbocaine (*dl* n methylpipecol 2 6 xylidide hydrochloride) Carbocaine, a further derivative of 2,6 dimethyl aniline, has been used clinically and demonstrated to possess good anaesthetic properties (Ekenstam and his colleagues, 1956) The hydrochloride is readily soluble in water and resistant to both alkaline and acid hydrolysis

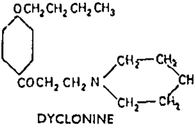
Mumford and Gray (1957) report its use in a series of dental cases and they found when carbocaine was used without adrenaline, it almost doubled the percentage of successful anaesthesias obtained with lignocaine under the same circumstances Further trials with adrenaline should prove interesting

Topical anaesthetics

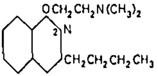
Pramoxine (*Tronothane*) (3 morpholinopropyl 4 butoxyphenyl ether hydrochloride) has been investigated as a surface anaesthetic and is claimed to have low sensitizing properties (Schmidt and his colleagues 1953)



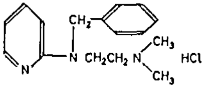
PRAMOXINE



DYCLONINE



DIMETHISOQUIN



TRIPELENAMINE HYDROCHLORIDE

Pramoxine is not an injection anaesthetic as it is relatively irritating However on topical application little evidence of irritation was observed even after a six weeks test on human volunteers in which pramoxine 1 per cent jelly was applied for 23 days continuously

Peal and Karp (1954) describe its use in proctology in which one ounce of a 1 per cent heavy jelly is applied directly to the operative site and following dressing a 1 per cent solution is sprayed from an atomizer on to the incision Relief from post operative discomfort was achieved in 68 per cent of patients

Similarly in obstetrics it is recommended to apply pramoxine jelly to episiotomy wounds and lacerations A light jelly was used with success for cystoscopy In some patients a transient burning was reported but disappeared before passage of the cystoscope

Dyclonine (*Dyclone*) (4 butoxy β piperidyl propiophenone hydrochloride) differs chemically from any of the local anaesthetics in use today Richards and his co workers (1952) demonstrated that Dyclonine is a potent surface anaesthetic on the cornea in rabbits and is free from toxicity

The drug has been investigated clinically (Harris Parry and Greifenstein 1956) It has been given to humans in doses from 200 to 500 milligrams by intravenous injection over a period of five minutes without affecting blood pressure heart rate or evidence of central nervous stimulation Nausea vomiting and dizziness were the only side-effects The drug thus possesses a low toxicity for humans

Owing to irritation on injection the drug is not of value for infiltration anaesthesia On topical application a 1 per cent solution results in good anaesthesia of the mucous membranes of the pharynx larynx and trachea lasting 20–25 minutes when volumes well below those giving rise to any toxic reactions are administered It is claimed that Dyclonine is a valuable drug for topical application with an exceedingly high safety margin

• In ophthalmic surgery Dyclonine though causing some congestion if used as a 1 per cent solution is as a 0 5 per cent solution, an excellent anaesthetic for intra ocular surgery There is also an absence of miosis or mydriasis and no increase of intra ocular tension Arora and Sharma (1955) claim that a single application of Dyclonine is as effective as four applications of 5 per cent cocaine or 1 per cent amethocaine •

Dimethisoquin (*Quotane hydrochloride*) [3 butyl 1 (2 dimethylaminoethoxyisoquinoline) hydrochloride]

Fellows and Macko (1951) found that dimethisoquin was a potent topical anaesthetic On the cornea of rabbits it was found to be ten times more active than cinchocaine Following intraperitoneal injection in rats it was half as toxic as cinchocaine On clinical use it is irritating to the eyes and should be kept away from the cornea In a 0 5 per cent solution or ointment it provides relief from skin irritation and pain from sutured skin wounds Following application its effects last for up to five hours It is claimed to have a low index of sensitivity (New and Non official Remedies 1955)

Antihistamines as local anaesthetics

While investigating the possibility that histamine was the chemical mediator of pain (Rosenthal and Minard 1939) it was demonstrated that antihistamine drugs had local anaesthetic properties Following the development of a large number of antihistamine drugs it was found that all had marked local anaesthetic properties (Keating and Code 1948)

Tripelennamine hydrochloride (*Pyribenzamine hydrochloride*) [2 Benzyldimethyl aminoethylaminopyridenehydrochloride] has been recommended as a topical

anaesthetic (Yonkmann and his colleagues 1949) This has been applied clinically by Reynolds Kahn and Levy (1950) who used an average of 30 millilitres of a 1 per cent solution for gastroscopy with no toxic reactions Fitzpatrick Orr and Stubbart (1952) employed a 2 per cent solution of pyribenzamine for urethral manipulations

When the drug is applied to the pharynx and the urethra burning has been reported which passes off as anaesthesia ensues Betcher and Tang (1955) following an assessment of 1 per cent pyribenzamine for potency by intradermal injections in human volunteers found the addition of adrenaline 1 100,000 increased the duration of the anaesthetic effect For local infiltration and regional nerve blocks for diagnostic therapeutic and surgical procedures, 1 per cent pyribenzamine was recommended However, following a brachial plexus block using 20 millilitres of solution in an adult Negro convulsions occurred which responded to oxygen and the administration of general anaesthesia It is suggested that pyribenzamine may be a useful local anaesthetic which is not only more potent but relatively less toxic than is procaine The frequent finding of drowsiness associated with its use is claimed to be an advantage

REFERENCES

Adler P Kesztyus L and Simon N (1950) *J dent Res* 29 713
Anderson E and Ruben J E (1952) *Anesthesiology* 13 429
Angerer A L Su H H and Head J R (1953) *J Amer med Ass* 153 550
Ansbro F P Iason A H Shaftel H E Halpern A Letteri F S and Bodell B (1952) *Anesthesiology* 13 306
— Blundell A E Sweeney J C Bodell B and Andorko J E (1954) *Curr Res Anesth* 33 406
Arora R B and Sharma V N (1955) *J Pharmacol* 115 413
Aven M and Foldes F F (1951) *Science* 114 206
Bartlett R W and Eastwood D W (1953) *J Amer med Ass* 152 1067
Batson O V (1940) *Ann Surg* 112 138
Bennett A L and Chinburg K G (1946) *J Pharmacol* 88 72
Bernhard C G and Bohm E (1954) *Experientia* 10 474
— — (1955) *Brit J Pharmacol* 10 288
— — and Hojeberg S (1955) *Arch Neurol Psychiat* 74 208
Betcher A M and Tang Z T (1955) *Anesthesiology* 16 214
Bonica J (1951) *Curr Res Anesth* 30 1
— (1957) *Anesthesiology* 18 10
Brink F Jr Bronk D W and Larrabee M G (1946) *Ann N Y Acad Sci* 47 457
Brodie B B (1956) *J Pharm Lond* 8 1
Bryce Smith R (1950) *Brit J Anaesth* 22 34
Buchi J (1952) *Arzneimittel Forsch* 2 1
Bullock K and Grundy J (1955) *J Pharm Lond* 7 755
Carney T P (1951) *Medicinal Chemistry* New York Wiley
Clarke R E Orkin L R and Rovenstine E A (1954) *Anesthesiology* 15 161
Conner E H and Dripps R D (1950) *Anesthesiology* 11 686
Council Reports (1949) *J Amer dent Ass* 38 148
Crawford O B (1953) *Anesthesiology* 14 278
Dornette W H L (1954) *Curr Res Anesth* 33 38
Doty R W and Gerard R W (1950) *Amer J Physiol* 162 458
Duncan D and Jarvis W H (1943) *Anesthesiology* 4 465
Eccles J C (1953) *The Neurophysiological Basis of Mind* London Oxford University Press
Eckenhoff K E and Kirby C K (1951) *Anesthesiology* 12 27
Ehrenberg L (1948) *Acta chem scand* 2 63

Einhorn A and Oppenheimer M (1900) *Liebigs Ann* 311 155
Ekenstam B Egner B Ulfendahl I R Dhuner K G and Oljelund O (1956) *Brit J Anaesth* 28 503
Fellows E J and Macko E (1951) *J Pharmacol* 103 306
Finer G H and Rovenstine E A (1947) *Anesthesiology* 8 619
Fitzpatrick R J Orr E M and Stubbart F J (1952) *J Amer med Ass* 150 1092
Foldes F F Davis D L and Plekss O J (1956) *Anesthesiology* 17 187
French J D Verzeano M and Magoun H W (1953) *Arch Neurol Psychiat* 69 519
Frey H H (1954) *Arch exper vet Med* 8 451
Frumin M J Schwartz H Burns J J Brodie B B and Papper E M (1953) *J Pharmacol* 109 102
— — — — — (1954) *Ibid* 112 387
Gaul L E (1955) *Anesthesiology* 16 606
Geddes I C (1955) *Brit J Anaesth* 27 610
— (1956) *Ibid* 28 55
— and Douglas D L (1956) *Fed Proc* 15 260
— and Quastel J H (1956) *Anesthesiology* 17 666
Goldberg L (1949) *Acta physiol scand* 181 1
Gordon R A (1943) *Canad med Ass J* 49 478
Graubard D J and Peterson M C (1949) *Anesthesiology* 10 175
Greene B A Berkowitz S Feldman E Goldsmith M and Robbins B (1956) *Anesthesiology* 17 165
Hancock E M and Cope A C (1944) *J Amer chem Soc* 66 1737
Harris L C Parry J C and Greifenstein F E (1956) *Anesthesiology* 17 648
Hazard R Corteggiani E and Pelou A (1944) *C R Soc Biol Paris* 138 427
Helrich M Papper E M Brodie B B Fink M and Rovenstine E A (1950) *J Pharmacol* 100 78
Hess A and Young J Z (1952) *Proc roy Soc* B 140 301
Hey P and Willey G L (1954) *Brit J Pharmacol* 9 471
Hodgkin A L (1951) *Biol Rev* 26 409
— and Huxley A F (1952) *Proc roy Soc* B 140 177
Holler W (1952) *Zahnar tl Welt* 7 247
Howarth F (1949) *Brit J Pharmacol* 4 333
Howland W S and Papper E M (1951) *Anesthesiology* 12 688
Kalman S I (1954) *Oral Surg* 7 1082
Kalow G (1952) *J Pharmacol* 104 122
Kato G (1936) *Cold Spr Harb Symp quant Biol* 4 202
Keating J U and Code C F (1948) *J Lab clin Med* 33 1096
Kelly M (1947) *Lancet* 1 710
Kendall C (1948) *J Amer med Ass* 138 599
Kohn J Rutter A G and Vitali M (1954) *Brit med J* 2 682
Krantz J C Jr Lu G and O Mally W E (1954) *J Pharmacol* 111 224
Laden E L and Wallace D A (1949) *J invest Derm* 12 299
Lane C G and Luikart R (1951) *J Amer med Ass* 146 717
Larrabee M G Posternak J M and Bronk D W (1947) *Fed Proc* 6 148
Linn J G Jr and Vey E K (1955) *Amer J Ophthal* 40 697
Lofgren N (1948) *Studies on Local Anaesthetics—Xylocaine* Stockholm Haeggstrom
Luduena F P and Hoppe J O (1952) *J Pharmacol* 104 40
Lundquist B Lofgren N Persson H and Sjogren B (1948) *Acta chir scand* 97 239
Lussier J J and Rushton W A H (1952) *J Physiol* 117 87
Mannheimer W Pizzolato P and Adriani J (1954) *J Amer med Ass* 154 29
Maykut M O and Ryan E A (1953) *Canad med Ass J* 69 419
Meidinger F (1945) *C R Soc Biol Paris* 139 907
Moore D C (1951) *Anesthesiology* 12 611
Mumford J and Geddes I C (1955) *Brit dent J* 98 200
— and Gray T C (1957) *Brit J Anaesth* 29 210
Muralt A (1954) *Ann Rev Physiol* 16 305
Mushin W W and Rendell Baker L (1949) *Lancet* 1 619

Nador K Herr F Pataky G and Borsy J (1953) *Nature Lond* 171 788
Nevin M I Epstein E and Nevin H R (1952) *Oral Surg* 5 1228
New and Non official Remedies (1955) Philadelphia Lippincot
Numans S K and Havinga E (1943) *Rec Trav chim Pays Bas* 62 497
Orkin L R and Rovenstine E A (1952) *Anesthesiology* 13 465
Peal L and Karp M (1954) *Anesthesiology* 15 637
Peterson, C G (1955a) *Anesthesiology* 16 678
— (1955b) *Ibid* 16 976
Quevauviller A (1952) *Prod pharm* 7 307
Reynolds J Kahn A G Jr and Levy J S (1950) *Gastroenterology* 14 535
Richards A Abreu B E Bockstahler E R and Wright D L (1952) *Fed Proc* 11 385
Rickles N H (1953) *Oral Surg* 6 375
Rosenthal S R and Minard D (1939) *J exp Med* 70 415
Roualle H L M (1952) *Brit med J* 2 1293
Rudin D O Fremont Smith K and Beecher H K (1951) *J appl Physiol* 3 388
Ryman B E and Walsh E O F (1954) *Biochem J* 58 111
— — (1955) *J Pharm Lond* 7 341
Sadove M S Levin M J and Rose R F (1954) *Curr Res Anesth* 33 366
Saker G and Shroder G (1954) *Anaesthesist* 3 359
Schlegel H E and Swan K C (1954) *Arch Ophthal* N Y 51 663
Schmidt J L Berryman G H McAndrews M J and Richards R K (1953) *Curr Res Anaesth* 32 418
Schoog M (1951) *Med Welt* 20 1622
Shanes A M (1948) *Science* 107 679
Shapiro S K and Norman D D (1953) *J Amer med Ass* 152 608
Sherif N A F (1930) *J Pharmacol* 38 11
Skou J C (1954) *Acta pharm tox Kbh* 10 281
Soehring K Kalm H Frey H H and Flinzberg G (1954) *Arch int Pharm* 99 188
Southworth J L and Dabbs C H (1953) *Curr Res Anesth* 32 159
Stampfli R (1954) *Physiol Rev* 34 101
Steinhause J E and Howland D (1957) *J Pharmacol* 119 186
Straub R (1956) *Arch int Pharm* 107 414
Tainter M L (1941) *Anesthesiology* 2 481
— Wessinger G D and Lee J W (1955) *J Amer dent Ass* 51 19
Tanz B Jaworski A A and Elkins L F (1951) *J Amer dent Ass* 38 148
Tasaki I (1939) *Amer J Physiol* 125 367
— (1953) *Nervous Transmission* Springfield Thomas
Ther L (1953) *Arch exp Path Pharmak* 220 300
Thorban W (1956) *Anaesthesist* 5 89
Toman J E P (1949) *Pharmacol Rev* 1 425
— (1952) *Ibid* 4 168
Trevan J and Boock E (1927) *Brit J exp Path* 8 307
Watts D T (1949) *J Pharmacol* 96 325
Weidling S (1948) *Acta pharm tox Kbh* 4 351
— (1952) *Anaesthesist* 1 119
Weinberg T (1952) *Sinai Hosp J (Baltimore)* 1 21
White C J Jr Dearborn E H and Swiss E D (1955) *J Pharmacol* 113 470
Wilson I B and Nachmansohn D (1954) In *Ion Transport across Membranes* Ed by Clark H T New York Academic Press
Yonkmann F F Roth F Smith J Hansen N and Craver B N (1949) *Curr Res Anesth* 28 170

CHAPTER 6

THE PLACE OF REGIONAL ANAESTHESIA IN ANAESTHETIC PRACTICE AND THERAPEUTICS

JOHN J BONICA

It is the purpose of this chapter to recount some of the recent advances and trends in regional anaesthesia to indicate its present status in practice and to suggest its proper role in surgery in obstetrics for diagnosis and in therapy of medical disorders The consideration of this method even at a time when the magic mixtures of muscle relaxants and intravenous barbiturates dominate the scene in world anaesthesia is unquestionably worth while for its clinical usefulness and advantages as well as its limitations and disadvantages are matters of controversy and keen dispute among anaesthetists (Bonica 1956c)

SUBARACHNOID BLOCK

Since the advent of the muscle relaxants the use of spinal anaesthesia for surgery has declined considerably A series of published reports of clinical survey has tended to show that the incidence of serious neurological complications is still frighteningly high (Thorsen 1947 Kennedy Effron and Perry 1950 Courville 1955) These reports had adverse effects not only on the public but on physicians including many anaesthetists who naturally questioned the propriety of using this method especially when a properly administered general anaesthetic together with muscle relaxants provided conditions similar to those produced by spinal anaesthesia The problem has been aggravated in some quarters by the number of medico legal suits which have been brought against physicians on account of complications that have occurred after spinal anaesthesia (Mushin 1954, Mair, 1954 Hunter 1956) some of which were minor and many of which were not related to the anaesthetic (Moore 1955) This trend has caused many anaesthetists in selecting the anaesthetic to consider the medico legal risk rather than the patient s welfare

Fortunately several recent outstanding studies have demonstrated the safety of this technique Arner (1952) surveyed the results of 21 230 cases Dripps and Vandam (1954) and Vandam and Dripps (1955 1956a 1956b) of 10 098, and Sadove and Levin (1954) of 10 000 spinal anaesthetics and found complications attributable to the anaesthesia extremely rare or non existent Moreover they found that the mortality from spinal anaesthesia was lower than that recorded after general anaesthesia Similar opinions concerning mortality with spinal anaesthesia were expressed by Schildt (1947) Kellum (1947) and Cole (1952) The last two writers studied published reports of 231,174 and 857 000 cases of spinal anaesthesia respectively More recently Macer (1956) *reported on* 37 391 spinal anaesthetics

given to obstetrical patients without any neurological complications or maternal mortality, and Moore (1955) has collected data that seem to substantiate the contention that the mortality is lower with spinal than with general anaesthesia He suggests that the incidence of neurological complication is no less following narcosis than after spinal anaesthesia

Causes of neurological damage

Recent data have demonstrated that the injected material rather than the lumbar puncture is the aetiological factor in the development of neurological complications (Arner, 1952, Vandam and Dripps, 1955 1956a, Moore 1955), and since it is generally accepted that the spinal anaesthetic drugs provided by reputable pharmaceutical houses are of a high standard attention has been focused on the modification of the technique to avoid the three possible causes of neurological damage (1) contamination of the anaesthetic solution (2) bacterial infection and (3) local toxicity caused by using improper therapeutic concentrations of the local anaesthetic drugs The last factor has been minimized by the definite trend to use smaller doses of drugs intrathecally The problem of contamination of the anaesthetic solution has been solved to a great extent by the now widespread practice of autoclaving all ampoules containing drugs for intrathecal injection instead of immersing them in antiseptic solutions This development constitutes without doubt one of the most important recent advances in spinal anaesthesia since it will obviate contamination of the drug by the antiseptic solution through cracked or imperfect ampoules which in past years has been considered a major cause of neuropathies (Galley 1951, Mushin 1954 Moore 1955) Reports of neurological sequelae developing from the detergent in which needles and syringes have been washed before being sterilized have also emphasized the importance of the proper preparation of the equipment prior to autoclaving (Winkelman 1952 Rendell 1954 Moore 1955)

Preparation of patient and anaesthetist

Since the subarachnoid space is no less vulnerable to bacterial infection than is the abdominal cavity, the preparation of both the anaesthetist and the back of the patient should be as thorough and painstaking as the preparation of the surgeon and abdominal wall The lumbar area should be shaved then cleansed with soap and water and finally treated with an antiseptic solution applied twice in the proper manner Chemical arachnoiditis due to seepage of the antiseptic solution along the side of the needle has been reported (Searles and Nowill, 1950) It is therefore essential to wipe the skin before the needle is introduced The use of an introducer with which to pierce the epidermis is also suggested so that no part of the spinal needle subsequently directed through it comes in contact with the skin The introducer also acts as a director and prevents the needle from buckling or deflecting It is therefore unnecessary for the anaesthetist to hold the part of the needle which is to enter the subarachnoid space and the risk of contamination is thus diminished

Technique of lumbar puncture

There has been little change in the technique of performing lumbar puncture since it was first described by Quincke in 1891 A number of recent publications (for example Macintosh 1951) have clarified many points concerning the

anatomy and have thus helped to refine the technique Others have re emphasized the value of the paramedian lateral and lumbosacral approaches in patients who have pathological changes of the spine which make the midline insertion impossible (Taylor 1940 Surks and Wood 1951 Ash 1955 Bonica 1956a) Although it is commonly agreed that maximum flexion of the spine facilitates lumbar puncture, some writers have recently suggested that the puncture be made with the patient in the *unflexed* position in order to decrease the incidence of headache (Rosser and Schneider, 1956) They claim that in this position, the hole made by the spinal needle is smaller because the posterior portion of the dura arachnoid is not under tension But their premise is based on inadequate studies and the increased difficulty of performing a puncture in this position and the consequent mental and physical trauma following repeated frustrating attempts neutralize any possible advantage of the technique

Use of finer needles

There is a definite trend to use finer needles in order to decrease the incidence of postspinal headache and cranial nerve palsies Although the exact mechanism for these vexing complications has not been demonstrated definitely the evidence that they are due to leakage of spinal fluid and consequent alteration in cerebro spinal fluid pressure is overwhelming (Wolff 1948 Bonica 1953 Vandam and Dripps 1956a) On the basis of this theory a number of clinicians have investigated the respective incidence of these complications following lumbar punctures with needles of various sizes Of the many reports that have been published the majority record a marked decrease in the incidence of complications following the use of fine needles (Harris and Harmel 1953 Greene Berkowitz and Gold smith 1954 Wetchler and Brace, 1955) A representative study by Greene (1950) indicated an incidence of headache of 10 per cent with 22 gauge needles 8 per cent with 24 gauge needles and 0 4 per cent with 26 gauge needles This writer also stressed the importance of adequate hydration in the prevention of this complication and recent studies indicate that the most effective active treatment of severe headaches consists of injecting saline solution in the epidural space *via* the sacrococcygeal or spinal route (Rice and Dabbs 1950 Bonica 1953) In order to obviate the greater difficulties in performing the puncture with the very slender needles Greene (1950) re introduced the double needle technique first suggested by Hoyt (1922) and Antoni (1923) who were among the first to appreciate the relation between the size of the puncture and incidence of headache Harris and Harmel (1953) reported an incidence of headache in 23 8 per cent of patients when 18 gauge or 16 gauge needles for continuous spinal anaesthesia were used 8 2 per cent with 20 gauge needles and 3 6 per cent with 24 gauge needles

Greene (1926) noted a decrease in the incidence of headache when a needle with a bevel possessing rounded rather than cutting edges was used Others (Hart and Whitacre 1951 Haraldson 1951 Cappe and Deutsch 1953) devised needles that have a rounded tapering point similar to the point of a finely sharpened pencil with the opening on the side of the needle just proximal to the solid tip Such a point separates rather than cuts the longitudinal fibres of the dura and thus decreases the size of the hole left in the membrane With these needles the incidence of headaches was halved

Spinal anaesthetics

The search for the ideal spinal anaesthetic has been continued unremittingly and a number of new agents, including lignocaine butethamine lucaine hexyl caine, 2 chloroprocaine and sympocaine have been given clinical trial Apparently none of these is sufficiently superior to those of the time tested standard preparations procaine amethocaine and cinchocaine Continued experience with simple solutions of these agents endorses the considered opinion that these drugs produce adequate spinal anaesthesia for the surgical procedures in which anaesthesia of this form is employed, and they are safer to use There is a trend to use hyperbaric solutions (Roman and Adriani 1949 Beecher and Todd 1954)

Several groups of agents not considered local anaesthetics have been given clinical trial for spinal anaesthesia Subarachnoid injection of barbiturates and antihistamines has been tried and found to produce sensory and motor anaesthesia but apparently the results were too variable and the complications encountered too serious to warrant further trial (Morrison Koppanyi and Tuohy 1951 Stephen and his colleagues 1954 Betcher and Tang 1955) In order to prolong the duration of spinal anaesthesia the practice of concurrently injecting intra thecally vasoconstrictor drugs with small therapeutic doses of standard local anaesthetic drugs has passed through several stages in recent years This practice, which was first suggested in 1900 by Braun (Braun 1905) became popular among clinicians and several well controlled studies concerning the action of these drugs were published (Sargent and Dripps 1949 Bonica Backup and Pratt 1951 Converse Landmesser and Harmel 1954) These indicated that adrenaline noradrenaline phenylephrine (neo synephrine) and methoxamine increased the duration of block by 50 per cent to 75 per cent but that ephedrine did not The numerous published clinical papers dealing with this subject contain only favour able results and none reports neurological complications In spite of these reports and notwithstanding recent animal studies which indicate that 10 to 100 times the therapeutic dose of these drugs needs to be injected to produce irreversible neurological change (Wu and his colleagues 1954), the possibility of producing such complications has deterred some anaesthetists from using this method at all and many others from using it except in very special cases At present it is the feeling of most anaesthetists that amethocaine or cinchocaine in small therapeutic doses produces anaesthesia of adequate duration for the majority of surgical operations This together with the ease with which a waning spinal anaesthetic can be supplemented with intravenous and inhalation drugs has decreased markedly the practice of intrathecal injection of vasoconstrictor drugs and of other methods of prolonging the duration of spinal anaesthesia including the fractional or continuous techniques

Continuous or fractional spinal anaesthesia

The introduction of the continuous or fractional technique by Lemmon in 1940 provided controllability of extent intensity and duration of analgesia and thus eliminated some of the most serious limitations and disadvantages of spinal anaesthesia It also opened new horizons for the use of spinal anaesthesia as a diagnostic and therapeutic tool The introduction of the ureteral catheter (Tuohy 1944) and other modifications further extended its usefulness However after early enthusiasm the continuous or multiple dose spinal anaesthesia technique has

suffered a gradual decline and today is used only occasionally (Beecher and Todd 1954 Lincoln and Fecteau, 1956) The reasons for such a marked decline are, first that the technique necessitates a larger puncture resulting in a higher incidence of headache (Lincoln and Fecteau 1956 Harris and Harmel, 1953) and secondly that the presence of the catheter in the subarachnoid space carries its own risks

Fractional segmental spinal anaesthesia

Fractional segmental spinal anaesthesia one of the modifications of continuous spinal first suggested by Saklad and his colleagues (1947) which entails the passage of a ureteral catheter cephalad for such distance as will place the tip near the nerve roots to be blocked, has not received serious consideration It is not being used because there is too great a risk that the catheter in being advanced may damage the spinal cord or in being withdrawn may avulse nerve roots around which it may have become looped (Brown, 1952 Bonica 1953 Alexander, 1954) The use of this technique for the injection of absolute alcohol as a therapeutic measure for intractable pain has also been reported (Ansbro 1950), but for the same reasons it has not been widely employed A technique for the precise segmental localization of a catheter orifice has also been described (Sarnoff, 1950)

Total spinal block

The use of total spinal block as advocated by Gillies and his associates (Griffiths and Gillies, 1948, Gillies, 1950 1952) in order to produce marked hypotension intentionally and thus reduce the blood loss during operation, has decreased since the advent of ganglionic blocking agents (Little 1956) However some still believe that in certain cases the spinal method is preferable for in addition to producing hypotension it provides analgesia for the operation and prevents undesirable reflex reactions without affecting the parasympathetic system as do the ganglionic blocking agents (Gillies, 1955)

Current and new trends

Finally a number of recent studies concerning spinal anaesthesia should be mentioned since they indicate current and new trends of thought By means of differential spinal block Sarnoff and Arrowood (1946 1947a) have resolved the controversy concerning the mechanisms of hypotension still the most frequent complication of spinal anaesthesia by demonstrating that it is primarily due to arteriolar dilatation consequent upon paralysis of vasoconstrictor sympathetic fibres For the treatment of hypotension during spinal anaesthesia a number of new vasopressors have been introduced which primarily affect peripheral vessels They include methoxamine (King and Dripps 1950) noradrenaline (Evans 1954b Churchill Davidson and Swan 1952 Eckenhoff and Dripps 1954) mephentermine (Smessaert and Collins, 1955) Oenethyl (Roman and Adriani 1944 LeCompte 1946), and methamphetamine (Dodd and Prescott, 1943 Anderson 1946 Dripps and Deming 1946) Of these noradrenaline has been shown to be the most potent while methoxamine produces the longest effect

The studies reviewed above have helped to place this method in its proper perspective (Hunter 1956) Today spinal anaesthesia maintains its position as the most practical and most frequently employed regional anaesthetic technique and many clinicians still favour it for selected patients who are to undergo operations

of the lower extremities, pelvis and back. In very recent years its use in obstetrics has increased markedly especially in the United States of America where it has been administered to many millions of mothers without serious complications. It has also received wide application as a diagnostic and therapeutic procedure. It is doubtful whether spinal anaesthesia will ever be abandoned as predicted.

SPINAL EPIDURAL BLOCK

Advantages

In the last several years there has been an increase of interest in the use of spinal epidural block, and much has been written about it including several monographs (Geldersen 1948 Bromage 1954 Groenendijk, 1954). Perhaps the most important factor to which this trend is due is the desire of some physicians to find a suitable substitute for spinal anaesthesia. Since the dura is not punctured and the solutions are not injected directly into the subarachnoid space headaches and cranial nerve palsies do not occur and the hazards of neurological sequelae theoretically do not exist. Moreover, in some instances a limited segmental block of the lower thoracic and lumbar region suffices, so that undesirable cardiovascular and respiratory effects are diminished and postanaesthetic dysfunction of the bladder, rectum and lower extremities is avoided. Epidural block requires only one puncture an advantage over multiple intercostal paravertebral or peripheral nerve blocks. Certainly it is preferable to extensive local infiltration or field block because it provides more complete analgesia and muscular relaxation requires less anaesthetic does not distort tissues and does not interfere with their post operative repair. Finally it affords longer post operative pain relief. The recent introduction of lignocaine, 2 chloroprocaine and hexylcaine, because of their activity penetrance and rapid action have minimized some of the serious disadvantages of extradural block. The feasibility of placing an indwelling catheter into the extradural space has further extended the clinical usefulness of this technique and has emphasized its superiority over regional methods which require multiple punctures since it affords much better control over the duration intensity and extent of the block. As the catheter does not come in contact with nerve elements the danger of exposing them to the constant irritation of a foreign body is eliminated—an advantage over continuous subarachnoid block. A final factor which has been responsible for the increased interest in spinal epidural block has been the appreciation of its considerable value as a diagnostic prognostic and therapeutic tool (Ciocatto 1953 Bonica 1953 Bonica and his colleagues 1957).

Disadvantages

In a recent communication based upon a survey of nearly 4 000 blocks and a review of the literature it was pointed out that spinal epidural block presents certain inconveniences hazards and limitations all of which must be recognized and appreciated (Bonica and his colleagues 1957). The technique of inserting the needle into the epidural space is more complicated and precise requiring considerably more skill and experience than does subarachnoid puncture notwithstanding the claims to the contrary of some enthusiasts (Dogliotti 1935 Gutierrez 1942). This is particularly true in the production of a segmental block in the thoracic or

cervical spine Moreover, there is a greater incidence of failures than with subarachnoid block, even in the hands of one equally proficient with both techniques In addition the onset of block after epidural injection is slower and more difficult to regulate than that after spinal anaesthesia Since the amount of local anaesthetic needed is 2 to 4 times that required with subarachnoid block, there is a greater risk of systemic toxic reactions and of a total spinal anaesthesia should the injection inadvertently be made into a blood vessel or into the subarachnoid space

Technique

In order to minimize or eliminate these disadvantages a number of refinements in technique has been suggested The oblique paramedian approach recently described is useful, especially in the midthoracic region or when the continuous technique is to be employed, because the angle at which the needle is directed greatly facilitates the passage of the plastic tubing or catheter (Bonica, 1956a) The proper identification of the epidural space remains the most critical aspect of spinal epidural block and a number of indicators for this purpose have been devised, including the Brunner Ikle spring syringe (Brunner and Ikle, 1949) the Macintosh balloon and spring loaded blunt canula (Macintosh, 1950 1953), and various manometers and glass indicators (Bromage 1954) These depend either on the presence of a negative pressure in the epidural space or on the sudden loss of resistance when the needle leaves the ligamentum flavum and enters this space Since recent studies (Bromage 1954, Bonica and his colleagues, 1957) indicate that in the lumbar region a negative pressure is present only in approximately 80 per cent of instances, loss of resistance is a more reliable indication in this area whereas in the upper thoracic and cervical regions the resiliency of the ligamentum nuchae and thinness of the ligamentum flavum make appreciation of this change extremely difficult Therefore, in these upper regions where there is almost always a negative pressure it is preferable to use a technique which depends on its presence Of the many pieces of apparatus to aid the visualization of this phenomenon the Macintosh balloon is the most reliable

Site of injection

Opinions as to the optimal site of insertion of the needle and the injection of solutions differ However, there is a trend to use the lumbar region except when a segmental block limited to the thoracic region is necessary for diagnosis or therapy Because of the difficulties in performing a puncture in the cervical region, there is a trend to avoid the use of this technique in this region

Volumes and concentrations of drugs

There has also been an obvious lack of agreement concerning volumes and concentrations of the drugs to be used However recent studies (Bonica and his co workers 1957) indicate (a) that volumes of 1 to 1½ millilitres of 2 per cent lignocaine hexylcaine 3 per cent 2 chloroprocaine, or equipenetrant solutions of other agents are sufficient to block one neurotome, and (b) that concentrations of lignocaine or equi active solutions of other anaesthetics required for various effects are as follows sympathetic block 0 3 to 0 5 per cent complete analgesia 0 5 to 1 per cent and complete motor block 2 per cent or greater There has been

a trend to take advantage of the differential blocking effects and to employ specific concentrations for each purpose

In some centres mixtures containing one of the newer, rapid acting more penetrant drugs such as 2 chloroprocaine and one of the older, longer lasting agents such as amethocaine or cinchocaine are employed, whereas in others the continuous technique is practised to avoid use of the latter 'more toxic drugs and to provide better control Recently Dogliotti and Ciocatto (1955) reported on differential peridural block which entails the constant subjection of mixed nerves to the action of concentrated local anaesthetics for several days They claim that this process produces partial degeneration of the sensory nerves and consequent relief of chronic pain American clinicians have been unable to repeat these results (Lewis 1956, Bonica and his colleagues 1957)

Studies concerning epidural block

A number of recent studies concerning spinal epidural block deserve mention Of interest are the studies concerning the site of block which heretofore has been considered to be in the intervertebral foramen and to involve the mixed spinal nerve distal to the point where the dura fuses with the epineurium These studies (Numans and Havinga 1943 Rudin Fremont Smith and Beecher 1951 Frumin 1954 and Frumin and his colleagues, 1953) suggested that the solution penetrates the dura and acts on the spinal nerve ganglia although subsequent information disputes this and supports the older theory (Foldes and Davis 1954, Scott 1956, Bonica and his colleagues 1957) Other studies have been concerned with the effects of epidural block on cardiovascular, respiratory hepatic and renal function as well as on the brain the uterus metabolism and the stress response (Bromage, 1954) The problem of hypotension with epidural block has been finally placed in proper perspective it is now fully appreciated that notwithstanding claims of earlier writers (Dogliotti 1939, Gutierrez 1942, Harger, Christofferson and Stokes 1941) to the contrary the incidence and magnitude of hypotension is the same with epidural block as with spinal anaesthesia and requires the same management (Bromage 1954 Scott 1956 Bonica and his co workers 1957) Other work has drawn attention to epidural block as a reliable clinical method of evaluating local anaesthetic drugs (Bonica 1957a Bonica and his colleagues, 1957)

OTHER REGIONAL BLOCKS

During the past five years there has been a decreased use of caudal anaesthesia for operations diagnosis and therapy, but a steady use of it for obstetrics

Peripheral nerve blocks including block of the brachial plexus sciatic and femoral nerves like all other regional techniques have been used less since the advent of muscle relaxants and intravenous barbiturates However the value of regional anaesthesia for surgery of the extremities is recognized The continuous technique for block of the brachial plexus (Ansbro 1946) has been found neither practical nor necessary (Bonica Moore and Orlov 1949) A continuous technique for sciatic block has been described (Cheeley 1952 Gross 1956)

Paravertebral blocks intercostal blocks field blocks or local infiltration which were formerly used in combination with light general anaesthesia in poor risk patients undergoing neck thoracic and abdominal surgery have been almost

completely abandoned This has been due to improvements in general anaesthesia, more frequent use of segmental epidural block, and a greater appreciation of the complications (hypotension and pneumothorax) and hazards (total spinal anaesthesia and neurological sequelae) of paravertebral blocks, especially in the thoracic region The high incidence of these complications has also discouraged the use of this technique as a diagnostic or therapeutic procedure despite the greater use of regional methods for this purpose A recent study by Moore and his associates (1954) investigated the mechanism by which myelopathies are produced after paravertebral and intercostal injection of neurolytic agents This was prompted by numerous reports of complications following injections of Efocaine They showed that these serious effects are not due to inadvertent subarachnoid injection of the solution into an unusually long cuff of dura arachnoid, as had long been contended, but to intraneural injection of the solution with consequent *central spread to the spinal cord along the perineural spaces but* within the epineurium

Intercostal block and local infiltration are now being employed as therapeutic measures more frequently than in former years (Bonica, 1953) Cranial nerve blocks for surgery were never popular and at the present time they are rarely done except for diagnostic or therapeutic purposes

There have been very few changes in the clinical use of topical anaesthesia which continues to have widespread use for various endoscopic procedures The value of the translaryngeal and transtracheal technique was recently re emphasized (Bonica 1949 Hayes, 1953) and subsequently has had widespread use A number of new topical anaesthetic agents have been employed extensively because of specific advantages These include lignocaine and hexylcaine with their rapid and profound action and pramoxine (Tronothane), which has a low toxicity and produces minimal primary sensitivity or cross sensitivity (Peal and Karp 1954) Two objective methods of evaluating topical anaesthesia in man one utilizing the laryngeal reflex and the other using electric currents in the urethra, have been described (Clark Orkin and Rovenstine 1954 Draper 1956)

A number of advances have been made in the use of blocks of the peripheral autonomic nervous system Recent studies with contrast media have demonstrated the facility of blocking the entire peripheral sympathetic outflow by placing a needle in each of three critical sites (Bonica 1953 1956b, Alexander, 1954) Ten to twelve millilitres of solution injected into the proper fascial plane in the proximity of the stellate ganglion spreads to involve the sympathetic chain from the middle cervical to the fifth thoracic ganglion so that all of the sympathetic fibres to the head neck, upper extremities and chest are interrupted Similarly, solution injected near the coeliac plexus spreads sufficiently to interrupt all of the sympathetic fibres to the abdomen and one with its tip at the anterolateral surface of the second lumbar vertebra interrupts all sympathetic pathways to the lower extremities and pelvis (Alexander and Lovell 1952, Bonica, 1953 1956b) In unusual circumstances diffusion from the lumbar region may be so widespread as to involve the entire ipsilateral paravertebral sympathetic chain (Egbert 1955) Although several techniques for stellate blocks have been described (Davies 1952 Bryce Smith 1952 Arnulf 1947, Moore 1954) there is a widespread trend to use the anterior paratracheal approach to the cervicothoracic chain (Findley and Patzer, 1945 Moore 1954 Bonica 1953) A modified technique and a lateral

approach to the lumbar sympathetic chain has been described (Bryce Smith, 1951, Wallace 1955) and a continuous method for paravertebral sympathetic block has been reported (Thomason and Moretz 1949, Betcher, Bean and Casten, 1953) Two relatively new techniques of ascertaining sympathetic interruption have come into widespread use especially in America (Bonica, 1953, Lewis 1955) One is measurement of skin resistance by means of a dermometer and the other involves the psychosympathetic reflex (PSR) which can be measured by employing an electrocardiograph

RECENT TRENDS IN AND PROPER PLACE OF REGIONAL ANAESTHESIA FOR SURGERY

In recent years there has been a marked decrease in the use of regional anaesthesia *for surgery in most clinics of Western Europe and of the two American continents* In addition to the factors mentioned in connexion with the specific techniques there are several other reasons for this trend, not the least important of which are the number of trained anaesthetists and the high standard attained in general anaesthesia which has made it more suitable for poor risk patients In the excitement of taking part in the many developments concerning general anaesthesia and becoming acquainted with them anaesthetists have abandoned regional techniques A cause and an effect of the comparative decrease in use of regional methods is the fact that many physicians conclude their training in anaesthesia having had little or no experience with regional techniques Hence in their practice they are uncertain of their use and, rather than risk a failure, abandon them The well trained anaesthetist ought to be able to administer both regional and general anaesthesia with equal competence, for the former is not only of special value in certain surgical and many obstetrical patients but is also more and more demanded for diagnosis and therapy of medical disorders

OPERATIONS ON THE HEAD AND NECK

There are a number of clinical applications for local and regional anaesthesia worthy of consideration (Hellijas and Tovell 1948, Macintosh and Ostlere, 1955) Lacerations of the scalp and simple depressed fractures in the presence of probable intracranial damage are best managed by this method Recently the value and necessity of regional anaesthesia has been demonstrated for craniotomy in patients in whom it is necessary to localize lesions prior to excision of the cerebral cortex for epilepsy (Penfield 1954 Pasquet 1954) and in aiding pyscho surgery (Lesse 1957) In post traumatic cases involving the face maxilla and throat it may be advantageous to have the patient awake with an active laryngeal and swallowing reflex Such is the case in simple fractures of the jaw which require wiring in tracheotomy for supraglottic obstruction and in helping to demonstrate an oesophageal diverticulum (Hellijas and Tovell 1948) Many surgeons still prefer the patient to be awake and talking in order to help detect damage to the recurrent laryngeal nerve during thyroidectomy and other operations on the neck Recently Tovell and his associates (Kay Tovell and Scoville 1954) reported the use of regional anaesthesia for the operative removal of ruptured cervical intervertebral disk in

168 patients emphasizing its superiority over general anaesthesia on account of the aid it gives the surgeon in identifying the involved nerve root and in preventing complications peculiar to this operation such as venous air embolism and quadriplegia Local infiltration and topical anaesthesia have maintained their primary position for many operations on the eye and for the simpler procedures involving the nose and contiguous structures (Fred, 1944, Dale, 1945, Atkinson 1955) Infiltration anaesthesia remains a useful method for adult tonsillectomy (Mousel 1941) Most small lesions of the tongue, lip and face are still being removed and numerous plastic operations are being performed with local field or nerve block

OPERATIONS ON THE EXTREMITIES

Regional anaesthesia has its greatest usefulness in surgery for patients who require operations on the extremities, because it affords more significant advantages for this purpose than for any other surgical application This is particularly true of brachial plexus block for surgery on the upper extremity, which when properly administered provides conditions which cannot be matched with any other form of anaesthesia (Bonica Moore and Orlov, 1949 Bonica and Moore 1950) The outstanding advantage is that, *properly administered*, it involves only a limited area without interfering with the function of other organs or structures It effects a specific and complete sensory blockade, and if muscular relaxation is necessary, complete paralysis may be effected, but the paralysis is limited to the extremity and does not interfere with muscles of respiration and thus precludes the need for controlled or assisted respiration and obviates the cardiovascular disturbances consequent thereto

Brachial plexus block

Brachial plexus block may be indicated for patients undergoing surgery on the upper extremities and who have complicating conditions such as shock, cardiac pulmonary hepatic or nerve disease, diabetes mellitus cerebro vascular disorders chest and head injuries and so on

The method under discussion is particularly applicable in older patients and in urgent situations when little is known about the patient or whenever it is necessary to operate on a patient with a stomach full of undigested food Whenever fluoro scopy or radiography is a necessary adjunct to the surgical procedure regional anaesthesia eliminates the danger of explosions respiratory depression or ob struction in the darkened room, and the patient is able to co operate with the surgeon

One of the most significant advantages to the patient of brachial plexus block is the minimal postanaesthetic nausea and vomiting and the immediate post operative analgesia made possible by the employment of one of the longer acting local anaesthetic agents such as Amethocaine The accompanying sympathetic block during this period may prove of value in the prevention or minimization of post operative reflex sympathetic dystrophy (Betcher, Bean and Casten 1953 Betcher and Casten 1955) All these factors permit earlier ambulation and oral feeding and consequently decrease the incidence of post operative pulmonary gastro intestinal and thrombo embolic complications

Furthermore, it is economical to use and, since the equipment is not bulky and can be transported easily, this technique is of special value in catastrophic conditions

The most important disadvantages of brachial plexus block are the slow onset of action failures in providing complete anaesthesia, and complications which occasionally occur Lignocaine, chloroprocaine and hexylcaine, because of their rapid action and superior penetrant powers, have greatly minimized the first two disadvantages and with experience and care complications should be minimal In recent studies the incidence of pneumothorax, which is by far the most important complication was found to be 1–2 per cent (Moore and Bridenbaugh 1954 Wishart, 1954 Dhuner, Moberg and Onne, 1955) Postblock neuropathy occurs only if the nerves are carelessly injured and if high concentrations of the anaesthetic are used (Moore 1955) Release of metallic ions from metal receptacles, syringes and needles, consequent to the action of the anaesthetic on those instruments has been suggested as an additional factor (Lundquist and his colleagues 1948 Wielding, 1948)

Sciatic and femoral nerve block

Block of the sciatic and femoral nerves for surgical anaesthesia of the foot and leg is not being used as widely as it should probably because of misconceptions concerning the difficulty, failures and complications In a recent review of over 800 cases Moore (1952) reported success in over 90 per cent of cases (even in the hands of physicians in training) and no complications The block is simple to execute, produces rapid anaesthesia of the foot and leg (except for its upper 5 centimetres) and affords all the advantages mentioned in connexion with brachial block Block of the lateral femoral cutaneous and obturator nerves is also needed for operations on the entire extremity Since this combination is more time consuming and the incidence of failure is higher because of greater difficulty in blocking the obturator nerve, it is rarely used, even by those who routinely practise regional anaesthesia Block of nerves at the knee or ankle can be employed in special cases but minor procedures are more frequently performed with light general anaesthesia

Extradural and subarachnoid block

Extradural block effected either *via* the sacrococcygeal hiatus (caudal anaesthesia) or by the spinal epidural route provides the advantages of peripheral nerve block and subarachnoid block without most of their disadvantages (Southworth and Hingson 1943) The continuous technique effected by inserting a catheter to the level of the first sacral or fifth lumbar vertebra (either by the spinal or caudal route) provides controllability of duration and intensity and is very useful in long operations (Bonica and his colleagues 1957) It may be employed to produce sympathetic block and relief of pain during the pre operative and post operative periods as well as for surgical anaesthesia in patients with vascular disorders (embolism) or severe trauma (Bonica 1953 1954a)

Single dose or fractional subarachnoid block limited to the lumbar and sacral segments is of course simpler to execute and produces more rapid anaesthesia than epidural block It is the most common regional technique employed for surgery of the lower extremity

OPERATIONS ON THE CHEST

The application of regional anaesthetic methods to the thoracic area is limited (Hellijas and Tovell 1948) and the present trend is to employ general anaesthesia Minor operations involving the breast or other structures of the chest wall may be best performed with regional anaesthesia, especially in aged or seriously ill patients (Seldon 1941a)

A combination of paravertebral block, brachial plexus block and infiltration has been the most widely used regional method for thoracoplasty (Wilson and Gordon 1952 Scurr, 1952) However, high spinal anaesthesia and segmental subarachnoid block have been advocated (Willanuer, Chodoff and Garcia, 1947 Hubbard, Schneider and Kenney, 1950) and in recent years there has been a significant increase in the use of segmental epidural block for thoracoplasty (Haglund 1951 Crawford 1952 Paletto 1952) and intrathoracic operations (Crawford 1952) With these techniques only analgesic doses of local anaesthetics are used in order to minimize paresis of the intercostal muscles In spite of their virtues none of these procedures has been employed widely This fact and personal experience with each of these procedures and general anaesthesia in over 600 patients suggests that the advantages are more apparent than real In spite of intensive psychological preparation, adequate premedication and complete analgesia the patients operated upon with only regional anaesthesia became apprehensive when the chest was opened They later became restless and began to move and interfered with the surgeon s task and frequently developed paroxysms of cough when the bronchial tree was manipulated Moreover, many of the patients who had epidural or subarachnoid block developed a degree of hypotension which caused concern and required treatment Patients undergoing intrathoracic operations do better with modern general anaesthesia, which affords optimal operating conditions for the surgeon and better control of the patient by the anaesthetist An examination of the post operative results with regard to incidence of spread, morbidity and mortality obtained with the general method in tuberculous patients shows them to be far better than those reported by the advocates of regional anaesthesia (Bonica and his colleagues, 1957)

ABDOMINAL OPERATIONS

The greatest decrease in the use of regional anaesthesia has occurred in surgery of the abdomen There are a number of factors responsible for this trend which are peculiar to this region

Although the benefits of regional anaesthesia in intra abdominal surgery have long been recognized and may be used as arguments for its use, each of the techniques presents certain disadvantages which have been important factors in their replacement by general anaesthesia in most surgical clinics Since these procedures except field and intercostal block *interrupt all* of the vasomotor segments which supply the splanchnic region a moderate to severe hypotension usually results Admittedly this may be managed successfully with vasopressors but it is still an important consideration particularly in patients in poor physical condition due to shock, hypovolaemia intestinal obstruction and cardiac disease

In addition there is paralysis of the lower intercostal muscles and consequent diminished tidal exchange which is compensated for by the conscious patient through an increase in the activity of the unaffected intercostal muscles and diaphragm (Crawford, 1952 Bonica and his colleagues 1957) Moreover, many patients undergoing operation on the viscera of the upper abdomen particularly the stomach, frequently experience discomfort and develop retching vomiting hiccoughs and occasionally cardiovascular and respiratory disturbances These reflex responses are due of course, to stimulation of unanaesthetized sensory pathways associated with the phrenic, vagus and sympathetic nerves They can be obviated by injecting these structures with a local anaesthetic but, unfortunately many surgeons are not adept with these procedures or do not want to bother with them so it then becomes necessary to administer light general anaesthesia and to use an endotracheal tube The general anaesthetic depresses the respiratory centre and homeostatic mechanism, so that respiratory compensation is diminished Assisted pulmonary ventilation is then necessary

In trying to select the best method for a patient the anaesthetist must compare the potential hazards inherent in the prolonged use of muscle relaxants with the potential hazards and possible disadvantages of the regional anaesthetic Assuming that the anaesthetist is capable of administering both methods equally well the patient and surgeon are the deciding factors If the surgeon is gentle in exploring the upper abdomen and if the patient s condition does not contra indicate an extensive vasomotor block regional anaesthesia offers some advantages On the *other hand, if the habits and behaviour of the surgeon are such that the patient* is likely to experience physical and mental discomfort during most of the operation, it is far better to use general anaesthesia from the beginning Certainly if the patient has shock, hypovolaemia or marked arteriosclerosis, it is best to avoid regional block because, although by using vasopressors one can maintain the blood pressure these patients fare much better with properly administered balanced anaesthesia

Although some points made in the preceding paragraphs apply to the use of regional anaesthesia for surgery of the lower abdomen there are significant differences that make this technique one of the better anaesthetic procedures for operations in this region Operations in the lower abdomen usually do not entail stimulation of the vagus and other unanaesthetized sensory nerves Moreover it is not necessary for analgesia to extend above the sixth or fifth thoracic neurotome so that there is a significantly less incidence of severe hypotension and intercostal muscle paralysis

OPERATIONS ON THE SPINE AND ADJACENT STRUCTURES

The advantages of regional anaesthesia for operations on the spinal column are well known and hypobaric subarachnoid block has been considered useful in this work for many years because it obviates the many problems inherent in general anaesthesia administered to patients in the prone position (Hellijas and Tovell, 1948) The same claims have been made recently for spinal epidural block (Bromage 1954 Groenendijk 1954 Crawford and his colleagues 1951 Tice, 1957) *Paravertebral block for this purpose has had its advocates (Seldon 1941b,*

Helliias and Tovell 1948) but it is more difficult and time consuming it requires multiple punctures and the results are less predictable

Segmental epidural block is by far the best anaesthetic method with which to perform spinothalamic tractotomy (Wester and Krumperman 1956 Bonica and his colleagues 1957) The segmental type of anaesthesia provides analgesia for the conscious patient and optimal operating conditions for the surgeon affording him an unparalleled opportunity for repeatedly testing sensations in the lower portion of the body during the course of the incision of the anterolateral quadrant of the spinal cord

PERINEAL OPERATIONS

In spite of the general trend to use less regional anaesthesia in surgery this method has maintained in many centres its position for surgery on the perineum and lower urinary intestinal and genital tracts (Tuohy 1941 Maidlow 1951 Evans 1954a Salvati and Kratzer 1956) Spinal anaesthesia and to a lesser extent caudal and spinal epidural block are preferred by many for transurethral perineal and suprapubic resections of the prostate for operations involving the urinary bladder and for gynaecological procedures on the perineum (Southworth and Hingson 1943 Morris and Candy 1957) Since most of these procedures are done on elderly patients whose pulmonary cardiovascular hepatic and renal function and also electrolyte fluid and acid base equilibrium are already burdened by age a regional block limited to the lumbar and sacral neurotomes avoids the systemic and psychological upsets which may attend general anaesthesia The use of the continuous technique enhances this method

This so-called saddle anaesthesia produced either by injections of hypobaric or hyperbaric solutions into the subarachnoid space or by injections into the sacral canal (caudal block) or lower lumbar epidural space is also useful for anorectal operations especially when the prone and Buei jack knife positions are used (Helliias and Tovell 1948 Parmley 1955)

REGIONAL ANAESTHESIA IN OBSTETRICS

(See also Chapter 11 for a review of current British practice)

Recent trends in the use of regional anaesthesia for obstetrics have varied greatly throughout the world Except for the United States of America Canada and a very few scattered medical centres in other countries this method is being used very little This trend is due to several factors related to obstetrical practice religious beliefs social customs and economic status In many countries the majority of deliveries are still performed by midwives without the benefit of anaesthesia (Bonica 1955) If analgesia is provided it is most commonly by means of inhalation administered either by the patient herself or by the midwife Even in circumstances in which most of the deliveries are performed by physicians in hospitals wherein the most advanced type of surgical anaesthesia is practised it has long been the custom to relegate the administration of obstetrical anaesthesia to a nurse intern or other physician untrained in this phase of medicine so that only the simplest (though not always the safest[1]) method is used Moreover anaesthetists inexperienced in regional anaesthesia discourage its use in obstetrics either on

mere theoretical grounds or because their inexperience has resulted in complications (Marston 1949)

In recent years there has been a trend in the United States of America and Canada for well trained anaesthetists to devote part or full time to the provision of service for obstetrical patients (Hellijas and Tovell 1948, Hingson and Hellman 1956 Webb and Leigh, 1953, Bonica and Mix, 1955, Rutherford and his colleagues 1956) The advent of better obstetric practices, antibiotics, blood transfusion and other advances has markedly reduced maternal deaths due to infection, haemorrhage and toxaemia and has thus brought anaesthesia into sharper emphasis as an important cause of death Moreover there has accumulated a great deal of evidence which indicates that, contrary to general opinion, the administration of anaesthesia is often more complex and requires more skill than do many surgical operations (Bonica and Mix, 1955 Crawford, 1956 Hingson and Hellman 1956) In obstetrics, it is necessary to consider in the choice and use of certain methods of anaesthesia not only that two lives are involved instead of one but that the special mechanical and physiological problems of pregnancy reduce the flexibility and margin of safety Moreover, women in labour frequently cannot be prepared properly and consequently present the additional hazard of the aspiration of gastro intestinal contents Medical complications such as toxaemias, as well as the irregular fashion in which these patients receive medication, constitute additional problems that often tax the efficiency of the obstetric team and justify the thesis that anaesthesia for obstetrics deserves the interest of the expert anaesthetist (Bonica and Mix, 1955)

Advantages

In obstetrics the outstanding benefit of regional anaesthesia is the lack of respiratory depression and other deleterious effects to both foetus and mother This consideration is particularly important for the premature or immature foetus or whenever obstetrical complications cause foetal distress Statistics have been published recently by Taylor and his colleagues (1951) who reported that no infants delivered with regional anaesthesia required resuscitation whereas 60 per cent of those delivered with general anaesthesia did require it Moreover he noted that an abrupt change from general anaesthesia to regional anaesthesia for caesarean section was followed by a rapid decrease in infant mortality from 19 per cent to 8 per cent (Taylor 1954) Similar statistics have been reported by others (Patten 1954 Judd 1954 Hellman and Hingson 1953) Regional anaesthesia also provides the mother with many benefits It precludes the danger of the aspiration of gastro intestinal contents into the tracheobronchial tree, which is a serious cause of maternal death with general anaesthesia (Hingson and Hellman, 1956 Parker, 1954, Lancet 1955 Collier 1956) It is therefore especially indicated in mothers who have taken food shortly before going into labour Moreover since uterine tone is maintained blood loss is less than with general anaesthesia and there is less nausea and vomiting and general morbidity

Pudendal block

These benefits can be obtained to a maximum degree with pudendal block used alone or combined with local infiltration (Klink, 1953 Kobak Evans and Johnson 1956 Hingson and Hellman 1956) Analgesia is usually adequate, the uterus fully

retains its tone and retracts promptly [illegible] the block is followed by tonic [illegible] on the foetus or the mother. The disadvantages of the technique are that it is more difficult and time consuming to execute, it is followed by a higher percentage of failures than saddle block and it does not provide relief from uterine contraction. Although these drawbacks with the exception of the latter have been minimized by the use of 1 per cent lignocaine, they are of sufficient significance to be the most important factor which has prevented the technique being used more extensively.

Other techniques

Other simple regional techniques which have been suggested for use in obstetrics include paravertebral block T_{11} and T_1 (Cleland 1933, Shumacker, Manahan and Hellman 1943, Jarvis 1944) and paracervical infiltration for uterine pain and infiltration anaesthesia for caesarean section (Beck 1942). None of these methods has been used extensively.

Regional methods in the form of caudal, subarachnoid and epidural block offer the mother other advantages. By effecting the continuous technique these may be employed to provide complete analgesia for the first stage of labour and intense anaesthesia for the second and third stage without depression to the infant. The intense perineal relaxation facilitates operative intervention and thus diminishes the hazards of delivery for both mother and infant. These methods are especially indicated in delivery of the occiput posterior, the large baby in transverse arrest and in multiple births. Moreover, the analgesia may be extended should caesarean section become necessary.

Subarachnoid block

Subarachnoid block is by far the simplest and one of the most effective methods for providing obstetrical analgesia and anaesthesia. Although this method has been advocated for many years (Cosgrove 1937, Maxson 1938) it has enjoyed more widespread popularity since Parmley and Adriani (1946) described the simple modified technique of saddle block. During the last decade many reports have been published containing accounts of its successful use in more than a million patients without serious complications (Schmitz, Towne and Baba 1949, Macer 1956, Moore 1956).

Its disadvantages are those of spinal anaesthesia in general, those most important being hypotension and postanaesthetic cephalalgia, which in obstetrical patients seem to occur more frequently than in surgical patients (Moore 1955, Hellman and Hingson 1956). Since the technique of saddle block with cinchocaine provides analgesia for 3–4 hours it may be used for the first stage of labour as well as for terminal analgesia. In the United States of America spinal anaesthesia is also the most widely used method for caesarean section (Helljas, Tovell and Holt 1947, Lull and Hingson 1948, Hingson and Hellman 1956) while continuous spinal analgesia, formerly used either for vaginal delivery or caesarean section (Ullery 1946), has been virtually abandoned for reasons previously given. In Britain this technique has not gained the same widespread use for this purpose because of the emphasis laid on the embarrassment of respiration which might follow spinal anaesthesia in patients with large abdominal tumours (Macintosh 1951). Certainly if the lower intercostal muscles become paralysed, ventilation is seriously impeded

However, this disadvantage can be minimized by employing small amounts of local anaesthetic drugs in concentrations which produce analgesia without muscle paralysis, which is not necessary for this operation

Caudal block

Caudal block has been popular in those regions where anaesthetic specialists provide services to obstetrical patients Although the single injection technique was formerly used (Baptisti, 1945) the advent of better equipment and drugs has resulted in an increased use of continuous caudal analgesia (Hingson and Edwards 1943 Hingson and Hellman, 1956) When skilfully administered to properly selected patients, it provides almost ideal conditions for both mother and infant It is particularly useful for mothers handicapped with severe heart disease, pul monary tuberculosis acute respiratory infections, metabolic disease diabetes mellitus, toxaemia and nephritis since it protects the mother from the stress and strain of labour and also protects the infant Its inherent dangers are infection and inadvertent spinal injection

Spinal epidural block

In recent years the use of spinal epidural block in obstetrics has been reported with increasing frequency (Hingson and Southworth, 1944, Crouch and Merry 1946, Flowers, 1954, MacMillan 1954, Bonica and colleagues, 1957) Both for vaginal and abdominal delivery it provides all the benefits of caudal and saddle block without many of their disadvantages It offers two significant advantages over caudal anaesthesia First less volume of the solution is needed Secondly, in the hands of an operator who can perform each of the two techniques with equal dexterity the incidence of failure is less with the lumbar epidural technique than with the caudal, because anomalies are less frequent in the lumbar spine than in the sacrum In addition, spinal epidural block produces subjective relief of labour pains more rapidly than when the solution is injected by the caudal route, probably because the site of injection is nearer to the sensory pain fibres of the uterus (Bonica and his colleagues 1957) On the other hand it is more difficult to master and may involve more serious complications since in the lumbar region it is easier to accidentally enter the dura than when the needle is inserted through the sacrococcygeal hiatus

Complications

It is well to re emphasize that to obtain all the aforementioned advantages of the various regional anaesthetic techniques it is necessary to realize some of their limitations disadvantages and complications Obviously this method is not applic able to all obstetrical patients Many uncomplicated cases may and should be treated with general analgesia and anaesthesia The administrator must be skilled not only in execution of the block but also in the management of the patient Since severe hypotension occasionally occurs it is essential to observe the patient closely and to take prompt action to avoid hypoxia of the infant as well as of the mother and possible serious consequences Most of the fatalities with these tech niques have been due to improper management of the patient after the block was completed Because of the concomitant vasomotor paralysis spinal, caudal or epidural techniques should be avoided in abruptia placenta or placenta praevia

because they may increase the haemorrhage. These techniques should be avoided also in patients who have diseases of the nervous system, marked anaemia, shock or impending shock, infection at the site of injection, or other conditions which contraindicate regional anaesthesia.

REGIONAL ANAESTHESIA FOR DIAGNOSIS AND THERAPY

The most important recent trend affecting regional anaesthesia has been the remarkable increase in interest and use of this method outside the operating room as a diagnostic, prognostic and therapeutic tool in the management of various diseases. At the present time many physicians recognize its value. The anaesthetist has attributes which make him the natural colleague to execute these procedures. He can contribute significantly to the solution of many difficult diagnostic and therapeutic problems, but he must assume responsibility and discharge his obligations as a physician rather than act as a technician, expert in inserting needles (Bonica, 1953, 1954b, 1954c).

Indications

Nerve blocks may be used as *diagnostic* procedures to secure information concerning the mechanism of the disease, to aid in differentiating visceral or somatic disorders that present confusing signs and symptoms, such as coronary occlusion and pancreatitis, and to determine whether pain is of visceral or somatic origin. The need for a thorough knowledge of various diseases to achieve a proper interpretation of the results is obvious.

Because of their reversible action these techniques are useful to ascertain the likely effects of surgical section, and thus facilitate the proper selection of patients. Moreover, such *prognostic* blocks afford the patient an opportunity to experience the numbness and other effects that will follow such procedures as rhizotomy, cordotomy and neurotomy. *Prophylactic nerve blocks* have a very limited role but may be used to prevent the dysfunction which may follow trauma, infection or operation (Betcher, Bean and Casten, 1953, Betcher and Casten, 1955). *Therapeutic nerve blocks* are effective in treating self-limited diseases accompanied by severe pain, to break up the so-called vicious circle of disease, and to provide symptomatic relief so as to permit other therapeutic measures or allow time for more adequate preparation of the patient prior to surgical operation. In patients with severe intractable pain or other disorders who are unsuitable for surgery, nerve blocks with phenol and alcohol effect relief for sufficient time to be of value (Bonica, 1953, Jones, 1957, Belam and Dobney, 1957).

BLOCKS OF THE AUTONOMIC NERVOUS SYSTEM

In recent years a vast amount of experimental and clinical evidence has been accumulated which indicates that interruption by regional nerve block of certain portions of the peripheral autonomic nervous system has beneficial effects in a great variety of disorders, including peripheral vascular disease, reflex sympathetic dystrophy, visceral disorders of the thorax and abdomen and certain musculoskeletal dysfunctions (White, Smithwick and Simeone, 1952, Betcher, Bean and Casten, 1953, Bonica, 1953, 1956d).

Peripheral vascular disease

Repeated or prolonged sympathetic block has been found of therapeutic value in patients with acute vasospastic disorders such as traumatic vasospasm acute arterial occlusion due to embolism or thrombosis, arterial aneurysm, acute thrombophlebitis circulatory insufficiency and the first phase of the immersion foot syndrome (Ochsner 1951 Gage and Ochsner, 1940, Ochsner and DeBakey 1941 Casten 1949, Thompson and Moretz, 1949 Lempke and Shumacker 1949 Steel 1951 Bonica, 1953 1956d Betcher, Bean and Casten 1953, Moore 1954 Mandl 1953, Lee 1955 Crandell and Page 1957) In chronic vasospastic disorders such as Raynaud s disease Raynaud s phenomenon acro cyanosis livedo reticularis third phase of the immersion foot syndrome vaso spasm associated with lesions of the spinal cord such as poliomyelitis and pyramidal disease and also in thromboangitis obliterans sympathetic blocks are of value only to determine the degree of vasospasm and to help predict the effects of sym pathectomy which is the procedure of choice (Telford 1944 Telford and Simmons 1946 Casten, 1949 Flothow 1951 White Smithwick and Simeone 1952 Bonica 1953b) Occasionally therapeutic sympathetic blocks are useful in manag ing chronic thrombophlebitis and chronic ulceration of the extremities (Mandl 1947 1953 Ochsner and DeBakey 1949 Ochsner and his colleagues 1950 Ochsner 1951 Ruben 1952 Crandall and Page, 1957, Belam and Dobney 1957)

Temporary blocks are of no therapeutic value and have little prognostic use fulness in degenerative diseases such as arteriosclerosis because maximal beneficial effects following sympathetic interruption frequently do not become apparent for days weeks or even months Although an improvement of circulation and walking tolerance following the block augurs well a negative response to the block does not necessarily indicate that the patient will not benefit from operation For patients with chronic vascular disorders who refuse or cannot tolerate an opera tion chemical sympathectomy produced with phenol or alcohol is an excellent substitute (Mandl 1947 Haxton 1949, Bonica 1953 Miles and Rothman 1954 Roedling and his colleagues, 1957)

Causalgia and other reflex dystrophies

Sympathetic blocks are of great value in managing sympathetic reflex dystrophy, the all inclusive term recently applied to a great variety of seemingly unrelated disorders previously considered under such terms as major causalgia post traumatic painful osteoporosis Sudek s atrophy post traumatic spreading neuralgia minor causalgia post traumatic pain syndrome sympathalgia shoulder-hand syndrome chronic traumatic oedema and reflex dystrophy (Bonica 1953) These syndromes appear to resemble each other in aetiology clinical manifestation and response to therapy and are characterized by excessive or unduly prolonged pain vasomotor and sudomotor disturbances delayed functional recovery and trophic changes (Livingston 1947 Bonica 1953 Casten and Betcher 1955) The aetiology may vary from a trivial injury to the severance of a major nerve, which serves as a focus constantly bombarding the spinal cord and activating central relays and implicating predominantly anterior horn cells (Livingston 1947 Betcher Bean and Casten 1953 Bonica 1953) The resulting sympathetic hyper activity initiates and perpetuates a vicous circle which must be interrupted in the acute stage before it causes irreversible trophic changes in tissues

Causalgia of the major type represents the most severe form of reflex dystrophy and is due to incomplete severance of a major peripheral nerve Sympathetic blocks almost always produce relief of the severe, burning pain and hyperalgesia (Livingston 1947 Leriche 1949 Bonica 1953) a response which is so constant that some authorities consider this as a cardinal diagnostic feature of causalgia (Doupe Cullen and Chance 1944) If sympathetic interruption is instituted promptly at the onset of the disorder it may produce prolonged relief, although in the majority of patients it will be necessary to do a sympathectomy in order to effect a cure (Doupe, Cullen and Chance 1944, Mayfield 1951, White Heroy and Goodman 1948) But even if the block fails to cure it is of value in affording the patient respite from his intense suffering and thus helps to prepare him for the operation

Repeated or continuous sympathetic blocks may be considered as the primary therapeutic measure in managing the acute phase of minor causalgia the shoulder-hand syndrome and other minor reflex sympathetic dystrophies (Homans 1940 1941, Evans 1947 Steinbrocker 1947, Mandl, 1947 Shumacker and Abramson 1949 Bonica 1953 Betcher and Casten, 1955 Belam and Dobney 1957) Their effect is less marked in the chronic phase of these disorders which then require intensive physical therapy as well as other forms of treatment (Roedling and his colleagues 1957)

Sympathetic nerve blocks may be of diagnostic and prognostic value in managing patients with phantom limb pain a condition considered by some as a form of reflex dystrophy (Livingston 1938 1947) and by others as a psychosomatic problem (Kolb 1954) In patients with predominantly burning pain, sympathetic blocks occasionally effect prolonged relief if used early (Livingston 1938 1947 Bonica 1953) but in most instances sympathectomy or better still, cordotomy is necessary (White and Sweet 1955)

Other disorders of the extremities

Sympathetic blocks are useful in predicting the effect of sympathectomy in patients with marked hyperhydrosis (White Smithwick and Simeone 1952 Bonica 1953 Moore 1954) They are also a valuable therapeutic adjunct to somatic block and physical therapy in the management of acute bursitis, tendinitis and other acute traumatic and infectious musculo skeletal disorders of the extremities (Bonica 1953) Sympathetic blocks are useless in managing chronic musculo skeletal disorders such as arthritis, ununited fractures and Charcot joint

Disorders of the head and neck

Although the French literature (Arnulf 1947 1954 Luzuy, 1946 Lambret Rozemon and Decoulx 1948 Leriche 1949) contains many glowing reports of the efficacy of cervicothoracic sympathetic (stellate) block in managing patients with migraine atypical facial neuralgia facial palsy hemispasm of the face tinnitis aurium obstruction of the central retinal artery due to embolism or thrombosis acute optic neuritis retinitis pigmentosa atrophic rhinitis and many other conditions of the head and neck in other hands this procedure has proved useless as a diagnostic prognostic or therapeutic measure (Bonica 1953 1956b) A small number of patients with hemiplegia due to cerebral thrombosis embolism or vasospasm have improved markedly soon after stellate block was completed

but, in view of the known vagaries of cerebral vascular accidents and their tendency for spontaneous recovery, these results are insignificant

Visceral disease

Since sensory fibres carrying impulses interpreted as pain reach the spinal cord by accompanying sympathetic nerves, block of the appropriate sympathetic nerves produces relief from pain as well as interruption of sympathetic function to the viscera (Mandl, 1947 White, Smithwick and Simeone 1952 Bonica, 1953 Moore, 1954) These procedures are indicated only when the pain is severe and intractable, such as occasionally occurs with angina pectoris, pulmonary embolism, acute myocardial infarction, aortic aneurysm acute pancreatitis, severe biliary or renal colic and other visceral disorders (Albanese and Pataro 1939, Marion 1945 Bonnet 1945, Rasmussen and Farr, 1946 Bageant and Rapee 1947 Gage 1948 Stubbs and Woolsey 1950 Rinzler, 1951, Eastwood and Womack, 1951 Ciocatto and Bruzzone 1952, White Smithwick and Simeone 1952 Howard Morgan and DeBakey, 1952, Bonica, 1953) Some writers believe that in addition to relieving pain these procedures improve the patient s condition by eliminating the visceral vasospasm and the greatly increased tone of smooth muscle which is usually present (Gage 1948)

Sympathetic interruption has also been suggested as a diagnostic and therapeutic measure for various other abdominal visceral disorders including congenital megacolon, spasm of the cardia, pylorus and other sphincters biliary dyskinesia post cholecystectomy syndrome coeliac ganglion syndrome, gastro intestinal pain of undetermined origin chronic pancreatitis, visceral crises of tabes idiopathic nephralgia intractable bladder pain orchitis salpingitis and dys menorrhoea (Luzuy, 1946, Esnaurrizar 1949) Although it is true that sympathetic block may provide temporary improvement, its value as a therapeutic measure is questionable

Sympathetic block has been employed successfully in management of reflex anuria and with dramatic beneficial effects in patients with eclampsia and other forms of toxaemia of pregnancy (Mandl, 1953 Lund 1951 Ostlere 1952 Bonica, 1953) It has also been used effectively as an added measure to somatic nerve block in patients with severe cancer pain which has a burning component (Dargent, 1948) Splanchnic block may provide temporary relief to patients who have severe visceral pain due to cancer (Bonica 1953 Jones 1957)

SOMATIC NERVE BLOCK

Regional block of somatic nerves is often indicated as a diagnostic prognostic or therapeutic procedure in managing severe neuralgia acute musculo skeletal pain cancer pain and in effecting interruption of peripheral sympathetic pathways (Bonica 1953 Lee 1955 Eckenhoff 1956) Since neuralgia is usually the symptomatic expression of a neuropathy myelopathy or disease of the brain and is the result of inflammatory circulatory toxic degenerative metabolic or neoplastic disturbance in sensory pathways it is essential to seek its cause carefully and to remove it if possible before blocks are instituted

Block of the cranial nerves is very useful in managing severe pain of the head and neck Block of the trigeminal nerve or one of its branches is especially useful

in treating the severe lancinating pain of tic douloureux or the severe pain of cancer (Harris 1940 Bonica 1953, Rollason 1955) Besides diagnostic and prognostic injections of local anaesthetics alcohol block of either the gasserian ganglion or one of the major branches of the nerve is a most useful palliative in patients who are not suitable for retrogasserian neurectomy, but alcohol injection should be avoided when surgery is likely to be undertaken Supra orbital infra-orbital and mental nerve block may be necessary in treating the severe pain of herpes zoster (Lee, 1955) Block of the glossopharyngeal nerve just below the jugular foramen is a very useful diagnostic and prognostic procedure in managing glossopharyngeal neuralgia, a condition which is characterized by sudden severe lancinating pain in the throat radiating to the angle of the jaw and occasionally to the ear and thyroid cartilage (Robson and Bonica, 1950 Bonica 1953) Infiltration or topical application of the trigger areas which are usually found in the tonsils pharynx or back of the tongue, also effect temporary relief The glossopharyngeal nerve has also been blocked for cancer pain of the throat and as a diagnostic procedure in carotid sinus syndrome (Bonica, 1953, 1954a) Superior laryngeal nerve block, either with local anaesthetics or alcohol is useful in managing severe neuralgia of the larynx and the facial nerve has been blocked for intractable spasm The vagus nerves may also be blocked in managing cancer pain of the larynx or lungs while the spinal accessory nerve may be injected to control spasm of the trapezius and sternomastoid muscles

Block of the cervical spinal nerves is a very effective measure in managing occipital and cervicobrachial neuralgia and musculo skeletal disorders of the shoulder and upper extremity and in controlling severe cancer pain of the neck shoulder and arm (Gage and Parnell 1947 Judovich and Bates 1949 Bonica 1953) Since all of the sympathetic fibres destined for the hand forearm and lower two thirds of the arm are carried by the brachial plexus block of this structure is a most effective measure to produce concomitant vasodilatation and analgesia in vascular disorders causalgia and other reflex dystrophies It may be employed to differentiate pain of peripheral origin from that caused by disorders of the central nervous system Blocking of the somatic nerves to any of the extremities results in weakness or paralysis and loss of proprioceptive and touch sensations thus producing a useless limb Obviously except in the extreme cases of patients with inoperable lesions prolonged blocks with alcohol or any other neurolytic agent are absolutely contra indicated

Block of some of the major branches of the brachial plexus are occasionally indicated Suprascapular nerve block is a most effective procedure in controlling severe pain of the shoulder joint due to bursitis tendinitis periarthritis arthritis acute post traumatic pain or any other cause (Wertheim and Rovenstine, 1941 Betcher, 1949, Skillern 1954) It is frequently combined with stellate block (Arnulf 1947 Gordon 1952 Moore 1954)

Paravertebral block of thoracic and lumbar nerves is useful in managing segmental neuralgia due to orthopaedic disorders infections or trauma (Judovich and Bates 1949 Lee 1955 Bromage 1956) It is also useful in controlling post-operative cancer pain and other musculo skeletal pain of the trunk This procedure is very effective in providing symptomatic relief to patients with acute herpes zoster (Findley and Patzer 1945, Lee 1955 Bromage 1956) Although it has been suggested that nerve block mitigates and shortens the duration of the disease

and reduces the incidence of post herpetic neuralgia, evidence that such is the case is lacking Post herpetic neuralgia is a complex and most difficult problem which usually cannot be affected by blocks or even by cordotomy (Bonica 1953 White and Sweet, 1955) Intercostal block is a very useful procedure in controlling post operative pain of the chest and abdomen, pain due to fractures of the ribs sternum or cartilages and pain of post traumatic or post operative neuralgia (Sampson and Fitzpatrick 1945, Richardson and Papper 1947, Bonica 1953 Belam and Dobney, 1957)

Sciatic nerve block can be used to control temporarily severe acute pain and to produce complete sympathetic interruption of the foot and leg in order to corroborate the effects of lumbar sympathetic block or as a therapeutic measure in patients with severe vasospasm and ischaemic pain (Marmer 1952, Cheeley 1952 Gross 1956) Block of the femoral, lateral femoral and saphenous nerves may be used as a temporary measure in controlling severe pain of the thigh and anteromedial aspect of the leg Lateral femoral nerve block has been used in diagnosis and treatment of meralgia paraesthetica (Bonica, 1953) Since the saphenous nerve is purely sensory alcohol block or avulsion can be performed safely to relieve severe pain of ischaemic neuritis or chronic ulceration Obturator nerve block is an effective diagnostic, prognostic and therapeutic measure in patients with severe pain in the hip joint and in patients with severe adductor spasm (Gross and Christie 1957) Block of the tibial or peroneal nerve or both at the level of the knee or ankle may be effected to produce analgesia and sympathetic block

CAUDAL AND SEGMENTAL SPINAL EPIDURAL BLOCK

Injection of local anaesthetic solution into the peridural space is one of the most effective means of producing interruption of somatic and sympathetic nerves and therefore can be used for any of the aforementioned indications Single and continuous caudal or lumbar epidural injections have been used for this purpose by many clinicians (Hingson and his colleagues 1947 Prosad 1954 Cleland 1952 Frere 1950 Orr and Warren 1950 Lund 1956 Berk and Krumperman 1952 Ciocatto 1953 Ciocatto and Bruzzone 1952 Thistlethwaite and his colleagues 1953 Walker and Pembleton 1953 Bromage 1954 Bonica 1953 Groenendijk 1954 Foldes, Colavinpenzo and Birch 1956 Bonica and his colleagues 1957) These blocks are particularly useful in certain patients with severe intractable cancer pain involving the lower portion of the body (Belam and Dobney 1957) The outstanding advantage of this technique is that a limited block involving any desired number of segments can be effected with only one injection and the effect can be extended for days or weeks by using the continuous technique

SUBARACHNOID BLOCK

Single dose or fractional subarachnoid block has been employed similarly as a diagnostic prognostic and therapeutic measure in various disorders involving the abdomen trunk and lower extremities Its value for this purpose has been increased by the introduction of the differential technique (Sarnoff and Arrowood

1946 1947a, 1947b Sarnoff, Arrowood and Chapman, 1948, Arrowood and Sarnoff, 1948)

Subarachnoid alcohol block when properly done produces a chemical posterior rhizotomy which compares favourably with surgical section Since Dogliotti (1931) first described it for the management of intractable pain, many reports have been published on this subject (Saltzstein 1938 Truelsen, 1943 Bonica 1954a) all of which indicate that it is an effective method for the relief of pain in patients unsuited for more radical neurosurgical operations It is particularly useful in relieving cancer pain caused by pressure on somatic nerves or nerve roots produced by metastatic lesions of the vertebrae and tumours in the paravertebral regions The duration of pain relief varies from several weeks to many months and sometimes years although in the average case its effects last 3 5 months (Bonica 1954a)

LOCAL BLOCK

Local block is especially useful in the diagnosis and treatment of acute and chronic cutaneous and musculo skeletal painful disorders such as ligamentous sprains, fractures bursitis tendinitis epicondylitis periarthritis certain forms of arthritis, low back pain acute torticollis and fibrositis (Leriche and Froelich 1936, Steinbrocker 1939 Travell 1949, Bonica 1953) This method is particularly useful in myofascial pain syndromes initiated or perpetuated or both by so called trigger areas in somatic structures (Bonica 1957b) These trigger areas develop consequent to accidental or surgical trauma infection and other disorders, and act as a constant focus of irritation In the majority of instances, injection of the focus which is not infrequently situated away from the area of pain reference, is followed by the disappearance of pain muscle spasm and vasomotor disturbances for periods that are much longer than the duration of anaesthesia It is essential, however that the trigger area be accurately located and injected In this connexion it is important to note that post traumatic and post operative scars may act as trigger areas even when not painful or tender Such trigger areas may also be located in the tonsils or peridental structures (Kretzschmar, 1956)

Ethyl chloride spray is also effective in these conditions when trigger areas are located in the skin or subcutaneous tissue (Kraus, 1941, Travell 1949, Travell and Rinzler 1952) Topical application is also very useful in managing acute pain of mucous membranes (Bonica 1953)

REFERENCES

Adams R C (1941) *Anesthesiology* 2 515
Albanese A R and Pataro V F (1939) *Sem med esp* 2 74
Alexander F A D (1954) Control of Pain Chap 28 *Anesthesiology* Ed by Hale D E Philadelphia Davis
— and Lovell B K (1952) *J Amer med Ass* 148 885
Anderson B M (1946) *Anesthesiology* 7 1
Ansbro F P (1946) *Amer J Surg* 71 716
— (1950) *Ibid* 79 276
— Gordon C A Bodell B and Latteri F S (1952) *N Y State J Med* 52 1901
Antoni N (1923) *Svenska Lakartidn* 20 529
— (1925) *Rev neurol* 1 619

Arner O (1952) *Acta chir scand* Suppl 167
Arnulf G (1947) *L Infiltration Stellaire* Paris Masson
— (1954) *Pratique des Infiltrations Sympathiques* Lyon Camugli
Arrowood J G (1950) *Proc R Soc Med* 43 919
— and Sarnoff S J (1948) *Anesthesiology* 9 614
Ash W H (1955) *Anesthesiology* 16 445
Atkinson W S (1955) *Anesthesia in Ophthalmology* Springfield Thomas
Bageant W E and Rapee L A (1947) *Anesthesiology* 8 500
Baptisti A (1939) *Amer J Obstet Gynec* 38 642
— (1945) *Amer J Obstet Gynec* 50 180
Beck A C (1942) *Amer J Obstet Gynec* 44 558
Beecher H K and Todd D P (1954) *A Study of the Deaths Associated with Anesthesia and Surgery* Springfield Thomas
Belam O H and Dobney J H (1957) *Anaesthesia* 12 395
Berk J E and Krumperman L W (1952) *Amer J med Sci* 224 507
Betcher A M (1949) *Bull Hosp Jt Dis* 10 233
— and Casten D F (1955) *Anesthesiology* 16 1003
— and Tang Z T (1955) *Anesthesiology* 16 214
— Bean G and Casten D F (1953) *J Amer med Ass* 151 288
Bonica J J (1949) *Anesthesiology* 10 736
— (1952) *J Amer med Ass* 150 1 and 581
— (1953) *Management of Pain* Philadelphia Lea and Febiger
— (1954a) *Anesthesiology* 15 134
— (1954b) *Ber f Nord Anaestesiol* Forenings 3 Kongras I Kobenhavn 11–12 June
— (1954c) *Proc R Soc Med* 47 1029
— (1954d) *J Mich med Soc* 53 167
— (1955) *Wisc med J* 54 501
— (1956a) *Anesthesiology* 17 626
— (1956b) *Dia méd* 28 329
— (1956c) *Wisc med J* 55 387
— (1956d) *Med Rec S Antonio* 50 245
— (1957a) *Anesthesiology* 18 10
— (1957b) *J Amer med Ass* 164 732
— and Mix G H (1955) *J Amer med Ass* 159 551
— and Moore D C (1950) *Curr Res Anesth* 29 241
— — and Orlov M (1949) *Amer J Surg* 78 65
— Backup P H and Pratt W H (1951) *Anesthesiology* 12 431
— — Anderson C E Hadfield D Crepps W F and Monk B F (1957) *Anesthesiology* 18 723
Bonnet G F (1944) *Gaz méd Fr* 2 230
— (1945) *Pr méd* 53 680
Braun H (1905) *Lokal Anesthesie* 1st Ed Leipzig Barth
Bromage P R (1954) *Spinal Epidural Analgesia* London Livingstone
— (1956) *Brit J Anaesth* 28 274
Brown S (1952) *Anesthesiology* 13 416
Brunner C and Ikle A (1949) *Schweiz med Wschr* 79 799
Bryce Smith R (1951) *Anaesthesia* 6 150
— (1952) *Ibid* 7 154
Cappe B E and Deutsch E V (1953) *Anesthesiology* 14 398
Casten D (1949) *Bull Hosp Jt Dis* 10 2 and Betcher A M (1955) *Surg Gynec Obstet* 100 97
Cheeley L N (1952) *Curr Res Anesth* 31 211
Churchill Davidson H C and Swan H J C (1952) *Anaesthesia* 7 4
Ciocatto E (1953) *Anaesthesist* 2 25
— and Bruzzone P L (1952) *G ital Anest* 18 241
Clark R E Orkin L R and Rovenstine E A (1954) *Anesthesiology* 15 161
Cleland J G P (1933) *Surg Gynec Obstet* 57 51
— (1952) *Curr Res Anesth* 31 5
Cole F (1952) *Anesthesiology* 13 407

Collier H (1956) *Brit J Anaesth* 28 130
Converse J G Landmesser C M and Harmel M H (1954) *Anesthesiology* 15 1
Courville C B (1955) *Curr Res Anesth* 34 313
Cosgrove S A (1937) *Curr Res Anesth* 16 234
Crandell D L and Page W G (1957) *Anesthesiology* 18 484
Crawford J S (1956) *Brit J Anaesth* 28 146
Crawford O B (1952) *N Y State J Med* 52 2637
— Ottosen P Buckingham W W and Brasher C A (1951) *Anesthesiology* 12 73
Crouch D M E and Merry E S M (1946) *Brit J Anaesth* 20 24
Dale H W L (1945) *Proc roy Soc* 38 624
Dargent M (1948) *Brit med J* 1 440
Davies R M (1952) *Anaesthesia* 7 151
Dhuner K G Moberg E and Onne L (1955) *Acta chir scand* 109 53
Dodd H and Prescott F (1943) *Surg Gynec Obstet* 77 645
Dogliotti A M (1931) *Pr med* 67 11
— (1935) *Trattalo di Anestesia* Torino Unione Tipografica Editrice
— (1939) *Anesthesia* Chicago Debour
— and Ciocatto E (1955) *Anesthesiology* 16 623
Doupe D F Cullen C H and Chance G O (1944) *J Neurol Psychiat* 7 33
Draper R (1956) Unpublished data
Dripps R D and Deming, M V N (1946) *Surg Gynec Obstet* 83 312
— and Vandam L D (1954) *J Amer med Ass* 156 1486
Eastwood D and Womack N A (1951) *Arch Surg* 63 128
Eckenhoff J E (1956) *J chron Dis* 4 96
— and Dripps R D (1954) *Anesthesiology* 15 681
Egbert, L D (1955) *Anesthesiology* 16 811
Esnaurrizar M L (1949) *J internat Coll Surg* 12 846
Evans F T (1944a) *Lancet* 1 15
— (1944b) Spinal Anaesthesia *Modern Practice in Anaesthesia* Evans F T Ed London Butterworth
— (1954a) *Modern Practice in Anaesthesia* Evans F T Ed 2nd Ed London Butterworth
— (1954b) *Practitioner* 173 433
Evans J A (1947) *Ann intern Med* 26 417
Findley T and Patzer R (1945) *J Amer med Ass* 128 1217
Flothow P G (1951) *West J Surg* 59 1101
Flowers C E (1954) *Anaesthesia* 9 146
Foldes F F and Davis D L (1954) *J Pharmacol* 110 18
— Colavinpenzo J W and Birch J H (1956) *Curr Res Anesth* 35 33 89
Fred G B (1944) *Ann Otol etc St Louis* 53 127
Frere R (1950) *Zbl Chir* 75 586
Frumin M J (1954) *Anesthesiology* 14 576
— Burns J J Brodie B B and Papper E M (1953) *J Pharmacol* 109 102
Gage I M (1948) *Surgery* 23 723
— and Ochsner A (1949) *Ann Surg* 112 938
— and Parnell H (1947) *Amer J Surg* 73 252
Galley A H (1951) *Lancet* 1 689
Geldersen C Van (1948) *Het Peridurale Block* Amsterdam DeBussy
Gillies J (1950) *Ann roy Coll Surg Engl* 7 204
— (1952) *Proc R Soc Med* 45 1
— (1955) Personal communications
Gordon E J (1952) *Sth med J Nashville* 45 1131
Greene B A (1950) *Anesthesiology* 11 464
— Berkowitz S and Goldsmith M (1954) *Anesthesiology* 16 302
Greene H M (1926) *J Amer med Ass* 86 391
Griffiths H W C and Gillies J (1948) *Anaesthesia* 3 134
Groenendijk H J (1954) *De Peridurale Anaesthesia* Amsterdam DeBussy
Gross G (1956) *Brit J Anaesth* 28 373
— and Christie J N (1957) *Curr Res Anesth* 36 (4) 4

Gutierrez A (1942) *Anestesia Extradural* Buenos Aires El Ateneo
Haglund G (1951) *Nord Méd* 45 14
Haraldson S (1951) *Anesthesiology* 12 321
Harger J R Christofferson E A and Stokes A J (1941) *Amer J Surg* 52 24
Harris L M and Harmel M H (1953) *Anesthesiology* 14 390
Harris W (1940) *Brain* 63 209
Hart J R and Whitacre R J (1951) *J Amer med Ass* 147 657
Haxton H A (1949) *Brit med J* 1 1026
Hayes J O (1953) *Curr Res Anesth* 32 213
Helljas C A Tovell R M and Holt K R (1947) *Anesthesiology* 8 113
— — (1948) *Anesthesiology* 9 400
Hellman L M and Hingson R A (1953) *N Y St J Med* 53 2726
Hingson R A and Edwards W B (1943) *J Amer med Ass* 123 538
— and Hellman L (1956) *Anesthesia for Obstetrics* 1st Ed Philadelphia Lippincott
— and Southworth J L (1944) *Curr Res Anesth* 23 215
— Whitacre R C Hughes J G Turner H B and Barnett J M (1947) *Sth Surg* 13 580
Homans J (1940) *New Engl J Med* 222 870
— (1941) *Ann Surg* 113 932
Howard J M Morgan T M and DeBakey M E (1952) *Surgery* 32 251
Hoyt R (1922) *J Amer med Ass* 78 428
Hubbard S T Schneider G F and Kenney L J (1950) *J thorac Surg* 20 43
Hunter A R (1956) *Curr Res Anesth*, 35 312
Jarvis S M (1944) *Amer J Obstet Gynec* 47 335
Jones R R (1957) *Curr Res Anesth* 36 75
Judd G L (1954) *J Amer med Ass* 156 1474
Judovich B D and Bates W (1949) *Pain Syndromes* 3rd ed Philadelphia Davis
Kay R Tovell R and Scoville W B (1954) *Curr Res Anesth* 33 52
Kellum J M (1947) *J med Ass Ga* 36 165
Kennedy F Effron A S and Perry G (1950) *Surg Gynec Obstet* 91 385
King B D and Dripps R D (1950) *Surg Gynec Obstet* 90 659
Klink E W (1953) *Obstet Gynec* 1 137
Kobak A J Evans E F and Johnson G R (1956) *Amer J Obstet Gynec* 71 981
Kolb L (1954) *Painful Phantom* Springfield Thomas
Kraus H (1941) *J Amer med Ass* 116 2582
Kretzschmar K L (1956) *Med Times* 84 516
Lambret O Rozemon L and Decoulx P (1948) *Technique de la Chirugie du Sympathique et de ses Infiltrations* Paris Doin
Lancet (1955) Editorial *Lancet* 1 956
LeCompte C B (1946) *Curr Res Anesth* 25 168
Lee J A (1955) *Brit J Anaesth* 12 584
Lemmon W T (1940) *Ann Surg* 111 141
Lempke R E and Shumacker H B Jr (1949) *Yale J Biol Med* 21, 321
Leriche R (1949) *La Chirurgie de la Douleur* Paris Masson
— and Froelich F (1936) *Pr méd* 44 1665
Lesse K T (1952) *Zbl f Chir* 77 1944
Lesse S (1957) *Curr Res Anesth* 36 (1) 41
Lewis L W (1955) *Curr Res Anesth* 34 334
— (1956) Unpublished data
Lincoln J R and Fecteau G O (1956) *Continuous Spinal Survey* Unpublished data
Little D M (1956) *Controlled Hypotension in Anesthesia and Surgery* Springfield Thomas
Livingston W K (1938) *Arch Surg* Chicago 37 353
— (1947) *Pain Mechanisms* New York Macmillan
Lull C B and Hingson R A (1948) *Control of Pain in Childbirth* 3rd Ed Philadelphia Lippincott
Lund I C (1951) *Anesthesiology* 12 613
— (1956) *Ibid* 17 605
Lundquist B Lofgren N Persson H and Sjogren B (1948) *Acta chir scand* 97 239

Luzuy M (1946) *Les infiltrations du sympathique* Paris Masson
Macer G E (1956) *West J Surg Obstet Gynec* 64 625
Macintosh R R (1950) *Anaesthesia* 5 98
Macintosh R R (1951) *Lumbar Puncture and Spinal Analgesia* 1st ed Edinburgh Livingstone
— (1953) *Brit med J* 1 398
— and Ostlere M (1955) *Local Analgesia Head and Neck* London Livingstone
Macmillan A (1954) *Canad Anaesth Soc J* 1 75
Maidlow W M (1951) *Anaesthesia* 6 164
Mair W (1954) *Anaesthesia* 9 242
Mandl F (1947) *Paravertebral Block* New York Grune & Stratton
— (1953) *Blockade und Chirurgie Des Sympathicus* Vienna Springer Verlag
Marion P (1945) *Lyon chir* 40 315
Marmer M J (1952) *Anesthesiology* 13 207
Marston A D (1949) Anaesthesia in Obstetrics in *Modern Practice in Anaesthesia* 1st Ed New York Haeber London Butterworth
Maxson L H (1938) *Spinal Anesthesia* 1st Ed New York Lippincott
Mayfield F H (1951) *Causalgia* Springfield Thomas
Miles E and Rothman J S (1954) *Amer J Surg* 87 830
Moore D C (1952) *J Amer med Ass* 150 550
— (1954) *Stellate Ganglion Block* Springfield Thomas
— (1955) *Complications of Regional Anesthesia* 1st ed Springfield Thomas
— (1956) *West J Surg* 64 667
— and Bridenbaugh L D (1954) *Anesthesiology* 15 475
— — Hain R F and Ward A (1954) *J Amer med Ass* 156 1050
Morris D D B and Candy J (1957) *Brit J Anaesth* 29 376
Morrison R L Koppanyi T and Tuohy E B (1951) *Anesthesiology* 12 315
Mousel L H (1941) *Anesthesiology* 2 61
Mushin W W (1954) *Anaesthesia* 9 233
Numans S R and Havinge E (1943) *Rec Trav chim* 62 497
Ochsner A (1951) *Curr Res Anesth* 30 61
— and De Bakey N (1941) *Tri St med J* 13 2654
— — (1949) *J Amer med Ass* 130 423
— — De Camp P T Richman I M Ray C J Llewellyn R C and Creech O (1950) *Surgery* 27 161
Orr R B and Warren K W (1950) *Lahey Clin Bull* 6 204
Ostlere G (1952) *Anaesthesia* 7 169
Paletto A E (1952) *Curr Res Anesth* 31 357
Parker R B (1954) *Brit med J* 2 65
Parmley R T (1955) *Saddle Block Anesthesia* Springfield Thomas
— and Adriani J (1946) *South med J* 39 191
Pasquet A (1954) *Curr Res Anesth* 33 156
Patten E L (1954) *J Amer med Ass* 156 1471
Peal L and Karp M (1954) *Anesthesiology* 15 637
Penfield W (1954) *Curr Res Anesth* 33 145
Prosad M (1954) *Anaesthesia* 9 177
Quincke H (1891) *Berl klin Wschr* 28 929
Rasmussen T B and Farr W J (1946) *J Neurosurg* 3 267
Rendell C M (1954) *Anaesthesia* 9 281
Rice G G and Dabbs C H (1950) *Anesthesiology* 11 17
Richardson D J and Papper E M (1947) *J thorac Surg* 16 432
Rinzler S H (1951) *Cardiac Pain* Springfield Thomas
Robson J T and Bonica J J (1950) *J Neurosurg* 7 482
Roedling H A Roth J M Osborn J E Schick R M and MacCarthy C S (1957) *J Amer med Ass* 165 799
Rollason W N (1955) *Brit J Anaesth* 27 354
Roman D A and Adriani J (1944) *Curr Res Anesth* 23 248
— — (1949) *Anesthesiology* 10 270
Rosser B H and Schneider M (1956) *Anesthesiology* 17 288

Ruben J A (1952) *Amer Practit* 3 569
Rudin D O Fremont Smith K and Beecher H K (1951) *J appl Physiol* 3 388
Rutherford R N Moore D C Dare J A and Rose P A (1956) *Amer J Obstet Gynec* 8 581
Sadove M S and Levin M J (1954) *Illinois med J* 105 169
Saklad M Dwyer C A Kronenberg S Neves E and Sorkin M (1947) *Anesthesiology* 8 270
Saltzstein H C (1938) *Int Clin* 3 167
Salvati E P and Kratzer G L (1956) *Surg Gynec Obstet* 103 434
Sampson P C and Fitzpatrick L J (1945) *Calif west Med* 62 254
Sargent W F and Dripps R D (1949) *Anesthesiology* 10 260
Sarnoff S J (1950) *Anesthesiology* 11 360
— and Arrowood J G (1946) *Surgery* 20 150
— — (1947a) *J clin Invest* 26 20
— — (1947b) *J Neurophysiol* 10 205
— — and Chapman W P (1948) *Surg Gynec Obstet* 86 571
Schildt E (1947) *Acta chir scand* 95 101
Schmitz H E Towne J E and Baba G (1949) *Amer J Obstet Gynec* 58 30
Scott D B (1956) *Brit J Anaesth* 28 187
Scurr C F (1952) *Curr Res Anesth* 31 225
Searles P W and Nowill W K (1950) *N Y St J Med* 50 2541
Seldon T H (1941a) *Anesthesiology* 2 194
— (1941b) *Ibid* 2 669
Shumacker H B and Abramson D I (1949) *Surg Gynec Obstet* 88 41
— Manahan C P and Hellman L M (1943) *Amer J Obstet Gynec* 45 129
Skillern P G (1954) *J Neurol Psychiat* 71 185
Smessaert A and Collins V (1955) *Anesthesiology* 16 795
Southworth J L and Hingson R A (1943) *Ann Surg* 118 945
Steel O C (1951) *Anaesthesia* 6 154
Steinbrocker O (1939) *Ann intern Med* 12 1917
— (1947) *Amer J Med* 3 402
Stephen C R Nowill W K Hall H Martin R and Margolis G (1954) *Anesthesiology* 15 601
Stubbs J B and Woolsey R D (1950) *South med J* 43 675
Surks S N and Wood P M (1951) *Anesthesiology* 12 239
Taylor E S (1954) *J Amer med Ass* 156 1481
— Govan C D and Scott W C (1951) *Amer J Obstet Gynec* 61 840
Taylor M D (1940) *J Urol* 43 561
Telford E D (1944) *Proc R Soc Med* 37 621
— and Simmons H T (1946) *Brit med J* 1 386
Thistlethwaite J R Edison T G Greenwold C and Harrison I (1953) *Surgery* 33 818
Thomason J R and Moretz W N (1949) *Surg Gynec Obstet* 89 447
Thorsen G (1947) *Acta chir scand* 95 Suppl 121
Tice W P (1957) *J Neurosurg* 14 1
Travell J (1949) *Miss Vall med J* 71 13
— and Rinzler S H (1952) *Postgrad Med* 11 425
Truelsen F (1943) *Acta chir scand* 88 17
Tuohy E B (1941) *Anesthesiology* 2 369
— (1944) *Ibid* 5 142
Ullery J C (1946) *Amer J Obstet Gynec* 52 100
Vandam L D (1956) *J Amer med Ass* 161 586
— and Dripps R D (1955) *Surgery* 38 463
— — (1956a) *J Amer med Ass* 161 586
— — (1956b) *New Engl med J* 255 843
Walker T and Pembleton W E (1953) *Anesthesiology* 14 33
Wallace G (1955) *Ibid* 16 254
Webb E and Leigh D (1953) *Curr Res Anesth* 32 199
Wertheim H L and Rovenstine E A (1941) *Anesthesiology* 2 541

REFERENCES

Wester R and Krumperman L W (1957) *Ibid* 18 316

Wetchler B V and Brace D E (1955) *Ibid* 16 270

White J C and Sweet W H (1955) *Pain Its Mechanisms and Neurosurgical Control* Springfield Thomas

— Heroy W W and Goodman E N (1948) *Ann Surg* 128 161

— Smithwick R H and Simeone F A (1952) *The Autonomic Nervous System* New York MacMillan

Wielding S (1948) *Acta pharm tox Kbh* 4 351

Willanuer G J Chodoff R J and Garcia J L (1947) *J thorac Surg* 16 438

Wilson H B and Gordon H E (1952) *Anaesthesia* 7 157

Winkelman N W (1952) *Neurology* 2 284

Wishart H Y (1954) *Brit J Anaesth* 26 120

Wolff H G (1948) *Headache and Other Head Pains* New York Oxford

Wu J J Harnagle D L A Brizzee K R and Smith S M (1954) *Anesthesiology* 15 71

CHAPTER 7

PULMONARY VENTILATION AND ITS CONTROL

A B DOBKIN

MODERN CONCEPTS OF NERVOUS FACTORS CONTROLLING PULMONARY VENTILATION

PULMONARY ventilation requires the inhalation and exhalation of air into and out of the lungs Although this exchange can be voluntarily controlled, respiratory movements are mainly controlled unconsciously and automatically by the complex centres in the central nervous system Legallois (1812) and Flourens (1842) noted that efferent impulses to the respiratory muscles originate in a respiratory centre in the medulla oblongata The essential area for control of breathing was localized anatomically to the reticular formation of the medulla (Pitts Magoun and Ranson, 1939)

Stimulation of the ventral reticular cells results in sustained inspiration (apneusis) Stimulation of the dorsal reticular cells results in sustained expiration If both are simultaneously stimulated sustained inspiration occurs The neurones of one area reciprocally inhibit those of the other with the inspiratory area being dominant Both centres have descending connexions with the motor neurones of the phrenic (C_{3-5}) and intercostal nerves (T_{2-6}) which run in the anterior columns and in the ventral part of the lateral columns of the spinal cord

Mechanisms influencing rhythmicity of respiratory centre

Four mechanisms may contribute towards the rhythmicity of the centre These are (1) reflexes through the vagus (Hall, 1836 Hering and Breuer 1868), (2) the constant stream of inspiratory influences which are periodically inhibited by extra medullary influence (Pitts, 1946) (3) periodic bursts of impulses inherently developed by the pontine and medullary centres (Hoff and Breckenridge, 1954), and (4) vagal activity at the supramedullary level (Kerr and his colleagues, 1954)

In summary the medullary cell masses may have intrinsic rhythmicity which is strongly influenced by pontine and supramedullary cells above and by vagal fibres below The primary control of respiration is probably located in the middle reaches of the reticular substance of the medulla These are uncircumscribed nuclear masses but have a general division into a more caudal ventromedial region which subserves inspiration and a more rostral, dorso lateral region which is predominantly expiratory in function It now appears that these centres are semi specialized parts of the extensive dorsal suppressor and ventral facilitatory systems of the reticular activating system of the brain stem The further clarification of the control of pulmonary ventilation by the brain requires careful exploration of the pons

(locus caeruleus) midbrain and other supramedullary regions (Hoff and Brecken ridge 1954 Kerr and his colleagues 1954, Baxter and Olszewski, 1955)

Central nervous system influences affecting the respiratory centre

There are three major groups of involuntary influences in the central nervous system which have a profound effect on the respiratory centre

(1) The most important are central chemoreceptors which are affected by the carbon dioxide tension and the hydrogen ion concentration (cH) of the blood supplying the medullary centres Specialized neural structures located in the medullary respiratory centres and exposed to capillary blood (not arterial blood) mediate this control This is a dominant mechanism for adjusting the pulmonary ventilation to the metabolic requirements of the body and will be considered more fully in the next section

(2) Body temperatures which vary a few degrees above or below normal may profoundly affect pulmonary ventilation in direct response to changes in body metabolism Thus a rise above 40 C causes severe tachypnoea a fall below 31 C may cause marked hypopnoea and below 28 C may result in apnoea The supramedullary reticular formation of the pons which ordinarily plays a second ary role to the vagus in determining the rhythm of respiration assumes a promi nent role when rises in body temperature increase the rate of breathing (Pitts 1949) In such circumstances it is likely that the pontine centre is receiving impulses from the thermoregulatory areas in the hypothalamus and that the control of respiratory activity in this instance is mainly at the hypothalamic level When on the other hand the body is cooled these impulses slow down and eventually cease at some critical level (25°–28 C)

(3) A third group of influences involves respiratory stimuli which are ill defined and unpredictable but nevertheless alter pulmonary ventilation for varying periods of time These involve the response to the reception of pain and changes associated with emotions and awareness The changes in respiratory patterns associated with pain emotional disturbances alterations in the level of consciousness and manic or depressive mental illnesses lack uniformity for analysis and do not show significant correlation with the type of emotional stimulus (Clausen 1951) Minor deviations from a normal placid state seem to evoke recognizable respiratory responses such as the rapid inspiration accompanying surprise the rapid and shallow breathing associated with pleasure the irregular sighing with anxiety states and multiple variations of respiratory responses to unpleasantness in some types of neuroses (Goldensohn 1955)

CHEMICAL CONTROL OF PULMONARY VENTILATION

It is evident from clinical research in man that acute hypoxia (8–12 per cent oxygen in the inspired air) causes a slight increase in pulmonary ventilation which persists after acclimatization (Rahn and Otis 1949) On the other hand the pulmonary ventilation does not change when the oxygen is gradually increased even until pure oxygen is inhaled The toxic symptoms which may develop if pure oxygen is inhaled for a prolonged period should not be forgotten (Davies and MacKinnon 1949 Comroe and Dripps 1950 Bean and Johnson 1955)

When carbon dioxide is added (up to 10 per cent) to the inspired air, the pulmonary ventilation increases almost tenfold When the carbon dioxide concentration is increased further, there is a progressive decrease in pulmonary ventilation which reaches normal at about 20 per cent inspired carbon dioxide The latter change is accompanied by a state of increasing general anaesthesia A further increase (30 per cent) causes convulsions (Meduna 1950) Voluntary forced breathing on the other hand, reduces the alveolar carbon dioxide tension below 40 millimetres of mercury and may, if continued, produce irregular breathing with a period of apnoea, dizziness and confusion (Brown 1953)

An acute change in the carbon dioxide tension in the arterial blood of man causes a corresponding change in the hydrogen ion concentration This is well seen during cyclopropane anaesthesia if the pulmonary ventilation is not assisted The rise of carbon dioxide tension with depression of pulmonary ventilation is rapid On the other hand, several minutes of vigorous breathing are necessary to lower an elevated arterial carbon dioxide tension to its original level (Dripps 1947, Buckley and his colleagues 1953)

The peripheral chemoreflex

Christensen (1954) has pointed out that if changes in pulmonary ventilation are to be studied on human subjects, one has to restrict the experimental conditions to what is clinically tolerated so that no harm may be done Animal experiments, however give limited information for when animals are anaesthetized the physiological changes induced are remote from normal Thus in fact we still know very little about the chemoreceptor reflexes controlling the pulmonary ventilation in man During the 10 year period from 1927 to 1936 Heymans and his colleagues demonstrated in animals the peripheral chemoreflex and pressor reflex mechanisms of regulation of the respiratory and cardiovascular centres in the brain stem Their work localized these peripheral receptors to the glomus caroticum and glomus aorticum (Fig 11)

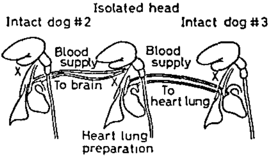


FIG 11 —Diagrammatic depiction of Heymans experimental arrangement to show peripheral chemoreceptor actions on pulmonary ventilation

Furthermore the Heymans studies emphasized that when the respiratory centres in the brain were deprived of peripheral chemoreflex nerve connections they still responded to increased carbon dioxide tension in the inhaled air and in the arterial blood This clearly proved that the brain centres have chemical receptors which react to changes in the arterial carbon dioxide tension (Heymans 1955 Heymans and De Vleeschhouwer 1956)

In 1951 De Castro distinguished the chemoreceptor and pressoreceptor nerve

fibres in the carotid area, and for the first time confirmed anatomically the original studies of Heymans and his associates

The role of the peripheral chemoreflex in the control of pulmonary ventilation has been the subject of intensive investigation since Heymans' work became common knowledge

The following observations are pertinent to this matter

In 1940 Gesell Lapides and Levin reported that the greater the carbon dioxide tension the less the effect on respiration of temporary blocking (cold) of the sinus nerve from the glomus caroticum and aorticum When the inspired carbon dioxide reached 5 per cent the chemoreceptors had no effect at all and respiration was controlled entirely by central drive

In 1940 Schmidt and Comroe and in 1943 Dripps and Dumke showed that the oxygen tension in the arterial blood rather than the oxygen saturation is the main factor affecting the peripheral chemoreceptor respiratory drive Moreover this chemoreceptor drive does not become manifest until the oxygen tension becomes quite low A man breathing an atmosphere in which the oxygen is reduced to 10 per cent (a tension of approximately 70 millimetres of mercury) responds with only a moderate increase in pulmonary ventilation (17 per cent) The maximum response (65 per cent increase) can be obtained by lowering the oxygen tension to 30 millimetres of mercury This hyperpnoea is due to chemoreflex stimulation of the carotid and aortic bodies On the other hand the respiratory centres themselves are unresponsive to mild hypoxia and are depressed by severe hypoxia

The converse applies to carbon dioxide The peripheral chemoreceptors are little sensitive to changes in carbon dioxide tension for when the carotid body is isolated from the general blood stream (to eliminate the effect on the respiratory centre) but its nerve supply retained a rise in carbon dioxide tension of 10 millimetres of mercury is required to produce even a slight increase in pulmonary ventilation On the other hand an increase of carbon dioxide tension by only 3 millimetres of mercury in the blood supplying the respiratory centre induces hyperpnoea It has therefore been concluded that the peripheral chemoreceptors do not play an active role in the control of pulmonary ventilation under normal conditions and that depression and ultimately failure of the central chemoreceptors is the dominant trend in severe hypoxia whereas the peripheral chemoreceptors retain their viability and continue to exert a stimulus response as the last line of defence

In 1941 Beecher and Moyer showed that during deep anaesthesia respiratory control is by the peripheral chemoreceptors and is absolutely dependent on slight hypoxia If oxygenation is normal or elevated the chemoreceptors become inactive and apnoea will ensue

In 1944 Banus and his colleagues proposed two different receptors in the respiratory centre one sensitive to pH in the interior of the cells themselves and the other sensitive to incoming reflex impulses The former is inactivated by anaesthesia and the latter is highly resistant to anaesthetic depression

In Sweden Bjurstedt (1946) Hesser (1949) Asmussen and Nielsen (1949) and Astrom (1952) contributed further to these studies by experiments on dogs Bjurstedt showed that acute hypoxia (6–8 per cent oxygen in nitrogen) is characterized by increasing respiratory alkalosis due to hyperventilation with a resulting decrease in activity of the central chemoreceptors due to the increase in pH of the blood (pH$=7\ 55$) The peripheral chemoreceptors were responsible for the increased pulmonary ventilation This peripheral drive gradually increased during the developing respiratory alkalosis thereby compensating for the decrease in central

chemoreceptor activity, until it was entirely responsible for the ventilatory drive Cold block of peripheral chemoreceptors at this stage caused apnoea

This confirmed the electrophysiological studies of von Euler, Liljestrand and Zotterman (1939) who also showed increasing action potentials from the carotid chemoreceptors during acute hypoxaemia In chronic hypoxia (8–12 per cent oxygen in nitrogen) the dominant stimulus of the peripheral chemoreceptors gradually decreased as the body compensated for the respiratory alkalosis (acclimatization) and the central chemoreceptors again became the active stimulus to pulmonary ventilation

Hesser (1949) attacked this problem slightly differently Central and peripheral chemoreceptors were studied in dogs during acid base displacements in the blood produced by administration of carbon dioxide–oxygen gas mixtures (respiratory acidosis) or by intravenous injections of N/2 hydrochloric acid (metabolic acidosis) or N/2 sodium bicarbonate (metabolic alkalosis) These studies showed that there was a time lag in the response of the denervated centre to changes in carbon dioxide tension and hydrogen ion concentration due to the time required for the cells of the centre to come into equilibrium with the blood These cells responded to induced metabolic acidosis (hydrochloric acid injection) with increased activity and to induced metabolic alkalosis (sodium bicarbonate injection) with decreased activity In acidotic conditions the response of the centre to carbon dioxide was increased and in alkalotic conditions the response of the centre to carbon dioxide was decreased When the peripheral chemoreceptors were intact, there was no change in these responses of the centre unless hypoxia was added, in which case ventilatory responses were increased

Astrom (1952) amplified the above studies using similar techniques and obtained the following results in dogs With spontaneous respiration the depth of barbiturate anaesthesia influenced greatly the ventilatory response to changes in carbon dioxide tension During deep anaesthesia hypoxia was the dominant ventilatory stimulus At high arterial pH hypoxia was a potent stimulus to pulmonary ventilation and its effect was produced via the peripheral chemoreceptors At low arterial pH the hypoxic chemoreceptor drive had only a minor share in the total respiratory activity Intravenous injections of cyanide produced a greater stimulation of respiration during low arterial pH than did the same doses at a high arterial pH

The action of combined hypercarbia and hypoxia in spontaneously breathing dogs was investigated The respiratory centre (peripherally denervated) was not immediately affected either by changes in the pH or oxygen saturation of the arterial blood The time lag observed for both carbon dioxide and oxygen was about three minutes The peripheral chemoreceptors on the other hand responded very promptly (in a few seconds) to changes in the oxygen saturation of the arterial blood and could be regarded as locally and functionally in the arterial stream If during hypoxia a high grade hypercarbia was added apnoea ensued because the depressed pH eliminated the peripheral chemoreceptor drive which was entirely responsible for pulmonary ventilation during hypoxia

On the basis of these studies Astrom proposed that there are two functionally different parts of the respiratory centre (1) a respiratory chemoreceptor which is depressed by anaesthesia in its reactions to changes in pH (carbon dioxide tension) although the centre still maintains its ability to respond to afferent impulses

from the chemoreceptors, and (2) a respiratory reflex centre which responds to impulses from the peripheral chemoreceptors (stimulus hypoxia) This centre is depressed by excess oxygenation but is resistant to anaesthesia This concept is similar to that proposed by Banus and his colleagues in 1944

In 1949 Gray attempted to integrate the present views on control of pulmonary ventilation as follows Carbon dioxide acting on the central chemoreceptors is the essential factor in ordinary quiet breathing (eupneic) This was the original concept of Haldane in 1905 (Haldane and Priestley, 1905) Nielsen s view that the carbon dioxide effect is specific and not due to its acidic properties was accepted (Nielsen and Smith 1951) During hypoxia the carbon dioxide tension falls and pH rises (hyperventilation) during metabolic acidosis the carbon dioxide tension falls and the oxygen tension rises, during carbon dioxide induced hyperpnoea the carbon dioxide tension and oxygen tension rise while the pH falls As an integrated explanation of these changes Gray formulated a Multiple Factor Theory Changes in carbon dioxide tension pH and oxygen tension may be additive or antagonistic the result being the algebraic sum of the individual actions Thus the hyperpnoea of metabolic acidosis causes increased elimination of carbon dioxide and lowers the carbon dioxide tension in the blood reducing the acidosis whereas during hypoxia the hyperpnoea improves tissue oxygenation

MECHANICAL FACTORS IN CONTROL OF PULMONARY VENTILATION

Christie and McIntosh (1934) Cournand (1950b) and Comroe (1953) and their co workers have presented the simplest approaches to this problem by dividing the mechanical factors in the control of pulmonary ventilation into those concerned with ventilation, diffusion and circulation With these are associated and must be considered the anatomical structures of respiration and their response to drugs and the reflexes which affect these anatomical structures to a degree which grossly alters pulmonary ventilation (Dawes and Comroe, 1954 Aviado and Schmidt 1955) Finally the application of external assistance or control of breathing requires a knowledge of the physiologically ideal respiratory pattern The pressure volume representation of the breathing pattern must be analysed as to the amplitude of pressure the ratio of duration of inspiration to expiration the contour of the curve and the rate of breathing per minute which are best for each patient (Cournand and his colleagues 1948 Otis Fenn and Rahn 1950 Fry and his colleagues 1954 McIlroy Marshall and Christie 1954 Dobkin and his colleagues, 1956 Gordon Frye and Langston, 1956)

Ventilation

The tracheobronchial tree

The tracheobronchial tree extends from the nares and lips to the respiratory bronchioles The exchange of gas between the outside air and the pulmonary alveoli must traverse this region in which no exchange of oxygen and carbon dioxide is possible From the orifices where air enters the respiratory tract down to the level in the trachea where it enters the thorax the airways are *inspiratory* check valves which manifest themselves by collapse of the nostrils on sniffing collapse of the

pharynx during sleep or during general anaesthesia (snoring) and closure of the larynx during swallowing and during light anaesthesia (laryngeal click) The intrathoracic airways are *expiratory* check valves which can be demonstrated fluoroscopically—the intrathoracic trachea and major bronchi shorten and narrow during passive expiration and exhibit marked degrees of collapse during cough the moment the glottis opens This may occur frequently under anaesthesia with an endotracheal tube in place Moreover, under certain conditions this intra thoracic expiratory obstruction can be rendered virtually absolute if sufficient negative pressure is applied to the airway The most important safeguard in this respect is adequate parenchymal recoil of the lung to keep the bronchioles open during expiration The elastic recoil of the surrounding lung parenchyma normally supports the bronchioles against check valve closure just as abductor muscles secure laryngeal patency during inspiration Complete loss of either safeguard is a major ventilatory disaster The effect of disease on these mechanisms is not completely known, but can be best demonstrated with the timed expiration recording, as shown by Dayman, (1951, 1956) and Franklin and his associates (1955) (Fig 12)

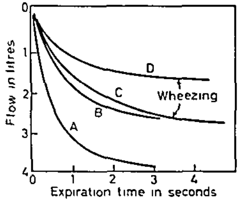


FIG 12—Pneumotachygraph tracing of a forced expiration by (A) normal patient (B) asthmatic patient (C) tuberculous patient with adherent pleura (D) elderly patient with emphysema *Note* The site of pathology in B C and D are differently located in the thorax but each causes a prolonged expiration time and increased residual volume (*after Dayman* 1956)

Bronchomotor tone

Daly Lambertsen and Schweitzer (1954) have demonstrated the direct central control of bronchomotor tone This is probably increased by chronic hypoxia and parasympathetic overactivity, and depressed by hypercarbia cervical vagotomy and atropine The tone of the bronchial tree is believed by Rodbard (1953) to play a major role in the control of gas exchanges and pulmonary circulation Christie and Bates (1955) noted that the ability of the normal lungs to follow the movements of the chest wall led to the statement that the elasticity of the healthy lung is perfect , therefore intrapulmonary pressure hardly alters during the ventilatory changes in lung volume However if the airways are partially obstructed because of increased bronchomotor tone or the presence of secretions or of inflammatory oedema the intrapulmonary pressure can be increased considerably This is caused by trapping of air in the alveoli and produces a stiff inelastic lung especially during expiration Prinzmetal and Kountz (1935) described these changes with the administration of histamine or during an attack of asthma Since pulmonary arterial pressure rises with increased intrathoracic pressure during expiration (25 millimetres of mercury) and falls during inspiration (10 millimetres of mercury) an increase in bronchomotor tone would enhance this effect and provide an in

creased resistance to flow through the pulmonary capillaries Pulmonary hyper tension would, therefore, develop and be most marked during expiration With increased bronchiolar tone, air entrapment may be progressive with successive respiratory efforts until the lung is filled with air under tension The alveolar capillaries are thereby compressed or obliterated so that blood flows through the lung with increased resistance The alveolar entrapment of air reduces the effective pulmonary surface area and gas exchange, causing hypoxaemia Since hypoxaemia increases pulmonary arterial pressure (constriction) and raises intrapulmonary pressure, a vicious circle is established (Baldwin, Cournand and Richards, 1949 Dayman 1951 Daly, Lambertsen and Schweitzer, 1953 Fry and his colleagues, 1954, Lucas 1955)

This mechanism has been implicated in the pathogenesis of emphysema, and may be one reason for decreased compliance of the lung during general anaesthesia

Respiratory dead space

In the anatomical sense, the 'dead space is that part of the respiratory tract occupied by gases which do not mix with those taking part in exchanges across the alveolar membrane In the functional sense the space is occupied by that expired volume of gas from the respiratory tract which did not, while in the lung take part in any carbon dioxide elimination (Fowler, 1952, Dripps and Severinghaus, 1955 Gray Grodins and Carter, 1956)

Under normal resting physiological conditions these two volumes are essentially equal During work and pathological conditions of the lung, however they are markedly different Rossier and Buhlman (1955) indicate that these differences depend on (1) changes in the anatomical dead space under the influence of drugs (2) the efficiency of gas exchange in the alveoli (3) the functional residual air and (4) dead space effects caused by uneven gas distribution and uneven pulmonary capillary blood flow, which upset ventilation and diffusion of oxygen and carbon dioxide

The dead space may be increased considerably during exercise owing to the lengthening and dilatation of the bronchi on inspiration and also in emphysematous patients who have a great increase in the functional residual air

The effect of anaesthesia on respiratory dead space is difficult to determine, because the pulmonary ventilation, body position and bronchomotor tone are altered In addition the open abdomen and surgical pneumothorax cause gross alteration in the pulmonary blood flow, particularly affecting the venous return to the heart (Hubay and his colleagues, 1954) At present the effects of only two of these factors have been really investigated (1) some drugs (atropine and ganglionic blocking drugs) can increase the anatomical dead space by 30 per cent whereas others by histamine release may decrease this space by about 10 per cent (Severinghaus and Stupfel 1955) and (2) variations of posture may decrease this space by anything up to 40 per cent (supine with head low) or may increase it (standing) (Rahn and his colleagues 1956, Attinger and his colleagues 1956a and b)

Functional residual capacity

The functional residual capacity (F R C) is the total volume of gas remaining in the lung at the end of a normal expiration In health the F R C amounts to 20–35 per cent of the total lung capacity (Whitfield Waterhouse and Arnott, 1950)

The clinical significance of an increased F R C is not clear at present since as Comroe and his colleagues (1955) noted older people have higher values (up to 50 per cent) without symptoms of cardiopulmonary disability It appears however that a reduction in this volume such as occurs in abnormal postures may be important in the control of pulmonary ventilation during clinical anaesthesia because the rate of change of anaesthetic depth and the rate of development of hypoxaemia and hypercarbia are increased

Distribution of inspired air and pulmonary capillary blood flow

Ideally the gas drawn into the lung is distributed evenly to all the alveoli and blood perfuses these alveoli equally in all parts Uniform distribution would therefore, require that during inspiration each alveolus should receive at the same time gas of the same chemical composition and of the same volume and that this gas should mix almost instantaneously with the functional residual gas in each alveolus (Fowler 1952, Comroe and his colleagues, 1955) Clinically however distribution is rarely uniform, even in a healthy subject, and varies considerably with postural changes Disease of the lungs causes further changes by regional alterations in pulmonary elasticity, bronchomotor tone, and bronchiolar secretions These obstruct blood and gas flow to varying degrees (Attinger and his colleagues 1956a and b)

Resistance and compliance

The work of breathing is a vital factor in consideration of the control of pulmonary ventilation McIlroy Marshall and Christie (1954), point out that 70 per cent is elastic work and 30 per cent is the non elastic work concerned with tissue deformation and air resistance (*see also* McIlroy and his colleagues 1955, 1956, McIlroy and Eldridge 1956 McIlroy Eldridge and Stone 1956 McIlroy and Marshall 1956)

The minimal work for a given ventilation is associated with a particular frequency of breathing The optimal frequency for minimal work with resting ventilation varies in individuals from 6 to 15 per minute and is increased for larger ventilation volumes (Otis Fenn and Rahn 1950 McIlroy Marshall and Christie 1954 Cournand and his colleagues 1954 Riley 1954)

Various components of this work have been studied recently An estimation of the over all function of the lungs must include measurement of these components which include (1) the work of the muscles ribs diaphragm and skin (2) the elastic resistance of lung tissue and (3) the viscous resistance of flowing gases (Dayman 1956)

Wade (1954) measured the linear displacements of various components of the chest during respiration by simultaneously tracing the radiographic shadow of each dome of the diaphragm recording a spirogram and measuring the chest expansion as well as the vertical movement of the thoracic cage Quiet respiration caused the diaphragm to move 1 5 centimetre while the chest circumference moved 1 2 centimetre when erect and 0 7 centimetre when supine One fourth of the vital capacity was attributable to chest expansion and three fourths was attributable to the diaphragm No evidence for voluntary control over the diaphragm alone was established

Under anaesthesia (spinal or general) with the upper abdominal cavity opened

the diaphragm appears to be almost motionless particularly when controlled breathing is used With spontaneous breathing it appears to move in longitudinal strands which never become very tense This is true also for the diaphragm on the open side of a surgical pneumothorax In both cases the diaphragm is not in a contracted state and becomes quite soft and doughy between contractions These clinical observations make it difficult to understand how adequate pulmonary ventilation can take place under anaesthesia with spontaneous breathing since 75 per cent of the gaseous exchange has been attributed to diaphragmatic activity

Jones Beargie and Pauly (1953) carried out electromyograph recordings of the intercostal and other respiratory muscles and showed that the intercostal muscles serve to keep the ribs at constant distances from each other, while the chest was expanded by the action of the scaleni and the diaphragm During quiet breathing the activity of the abdominal muscles was relatively small

Ventilatory changes during the various mechanical changes in the lungs depend on the static and dynamic resistance characteristics of the air passages and the lung parenchyma The static resistance of the lung parenchyma depends primarily on its elastic properties or compliance This is easily measured during anaesthesia With the patient supine and a cuffed endotracheal tube connecting the patient to an anaesthetic machine with nondistensible tubing the lungs are inflated from the reservoir bag The bag is closed at its inlet the pressure is measured and then the expiration is passed to a rapid writing kymograph and spirometer The compliance is determined by dividing the volume of air collected (in litres) by the pressure change (in millimetres of mercury) By measuring compliance at different pressures an S shaped curve is obtained which is steepest in the 2 to 4 litre range If the subject is awake and seated if the resistance to flow is normal (1 to 3 millimetres of mercury) and if the functional residual capacity is normal the lung volume will change about 120 millilitres per second for each millimetre of mercury change in pressure Under anaesthesia compliance usually varies between 65 and 80 millilitres per second per millimetre of mercury if the lungs are normal and the subject is supine The latter figures may represent the true compliance of the lungs as subjective factors in measurement are eliminated by anaesthesia

Resistance is measured under dynamic conditions and indicates the viscous or frictional (turbulent) impedances to airflow These may be measured by a pneumo tachygraph and pressure gauges attached to the airway to determine the pressure required for gas flow between the mouth and the alveoli (airway resistance) as well as an oesophageal balloon attached to a sensitive pressure manometer to determine the transmitted pulmonary tissue resistance The total resistance (airway plus tissue) is calculated by dividing the pressure change from air entry by the volume of air entry per second (Mead and Whittenberger 1953 Wu Miller and Luhn 1956)

The airway is responsible for 80 per cent and the normal lung tissue for 20 per cent of the total resistance (Comroe *and his colleagues* 1955) As noted in the discussion on the tracheobronchial tree in a patient under anaesthesia these resistances assume great importance if the patient has asthma bronchitis or emphysema or if the airway is partially obstructed during depressed ventilation A knowledge of these factors is essential to the clinical anaesthetist who uses controlled pulmonary ventilation with the aid of a mechanical respirator Disaster lies ready for him if the mechanics of his respirator or of his patients lungs or both, are unknown!

Spalding (1955) has shown in the paralysed patient with healthy lungs that during inflation the tidal volume is proportional to the inspiratory pressure between tidal volumes of 275 and 1100 millilitres and peak pressures of 9 to 25 centimetres of water The duration of inspiration influences the tidal volume optimally at about 1 5 seconds With a peak pressure of 15 centimetres of water, 480 millilitres of air enter the lungs in the first 0 7 seconds and 190 millilitres enter in the next 0 7 seconds, provided the gas is supplied at an airflow exceeding 40 litres per minute (Pask, 1955)

As noted by Christie (1953), the rate and depth of ventilation are also important in considering both the work of breathing and the alveolar ventilation This relation ship is shown in Fig 13 for an alveolar ventilation of 3 6 litres per minute

In reviewing the current physiological literature on lung compliance and resis tance the anaesthetist must bear in mind that any decrease in compliance and increase in resistance is likely to indicate decreasing ventilation due to developing patchy atelectasis or airway obstruction, rather than any effect the anaesthetic drugs may have on the lung parenchyma

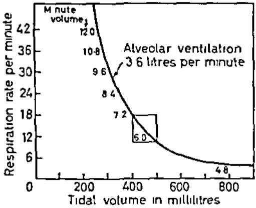


FIG 13—Resting healthy adult male height 173 cm weight 72 kg BSA 1 86 in supine horizontal position Premedica tion pentobarbital 100 milligrams atro pine 0 6 milligram In order to maintain efficiently an alveolar ventilation of 3 6 litres per minute in this case the rate of respiration should be between 12 and 18 per minute with a minute volume of pulmonary ventilation between 6 0 and 7 2 litres per minute During operations with surgical pneumothorax the faster rate should be used because of increased airway resistance and decreased lung compliance

Recently a number of investigators have attempted to reduce the mechanical factors involved in pulmonary ventilation to simple mathematical principles as for example Poiseuille s Law (Gray 1949 Otis and his colleagues 1956 Perkins Adams and Flores 1956) However, pulmonary ventilation occurs by an alter nating somewhat pulsatile gas flow which is never steady or streamlined The flow throughout the tracheobronchial tree is turbulent rather than laminar The bronchi are neither straight nor rigid and the viscosity of the gas (which is not homogeneous) progressively increases and decreases as it flows into and out of the lungs It therefore appears ludicrous at this stage of our knowledge to apply orderly expressions to such disorderly events

Diffusion

Oxygen and carbon dioxide must cross two membranes—alveolar and capillary (Low 1952) The surface area of the alveolar membrane is estimated at 50 times the body surface area (Comroe and his colleagues 1955) Its characteristics depend on its area thickness and functional activity This value is described physiologically as the Apparent Diffusing Capacity of the lung (D) and is defined as the number of millilitres of gas transferred per minute for each millimetre of mercury pressure

gradient across the membrane (Lilienthal and Riley 1954) Until recently D was measured using carbon monoxide or oxygen

Bates (1956) has summed up the established knowledge of gas diffusion and its importance in control of pulmonary ventilation as follows

> The normal resting diffusing capacity is about 21 millilitres per minute per millimetre of mercury with oxygen (Lilienthal and his colleagues 1946) and 17 with carbon monoxide (Krogh 1915) The diffusing capacity increases by about 75 per cent on exercise and usually reaches its maximum well before the limit of effort or of oxygen uptake has been reached The diffusion capacity is greater in persons with a large lung volume Increasing age reduces the diffusion capacity In a normal lung the ratio between contained gas volume and the rate of diffusion is not constant and the measured overall rate of diffusion depends on the ratio between ventilation and diffusion in different parts of the lung Gross disturbances of gas diffusion in disease may be sufficiently great to affect lung function (Cournand 1950a and b) (Table I)
>
> Severe impairment of gas diffusion may show itself by excessive ventilation for a given oxygen uptake by arterial unsaturation on exercise and by limiting the maximum oxygen uptake to a very low figure Although the methods for measuring pulmonary diffusing capacity are still very complicated Bates believes it has value in clinical studies of patients with pulmonary emphysema in cases of obscure pulmonary infiltration and in cardiopulmonary disease such as left ventricular failure with pulmonary congestion

Two special phenomena occurring in relation to anaesthesia depend partly on oxygen and carbon dioxide diffusion in the lungs One has in fact little to do with diffusion whereas the other is wholly dependent upon normal lung diffusion The first was named diffusion respiration by Draper Whitehead and Spencer (1947) Respiratory movements were abolished after denitrogenation with pure oxygen (45 minutes) using thiopentone relaxant anaesthesia Survival of the animal in complete apnoea was alleged to be due to an inward current of oxygen replenishing the alveolar oxygen which has diffused into the circulating blood by the so called oxygen haemoglobin pump mechanism This inward flow and diffusion of oxygen is probably a minor factor and bare survival for up to one hour in animals and man can be explained by two complementary mechanisms (a) cardiac activity causing some air exchange between the alveoli tracheobronchial tree, and the ambient air and (b) the oxygen taken up in the denitrogenation procedure has filled the lungs with oxygen fully saturated the plasma and haemoglobin of the blood and oxygenated the tissues and the myoglobin The reduced metabolism during anaesthesia and during apnoea could alone allow up to 45 minutes survival without added oxygen It seems doubtful whether, in fact, the oxygen haemoglobin pump mechanism exists In these experiments the carbon dioxide elimination from the alveoli comes to a virtual standstill in the absence of respiratory movements and the alveolar carbon dioxide gradually rises to extremely high levels This effect is similar to that which occurs during insufflation of anaesthetic vapours with oxygen during depressed pulmonary ventilation

The second phenomenon was called ' diffusion anoxia by Fink (1955), who explained the development of hypoxia at the end of an anaesthetic with nitrous oxide and oxygen as follows Large volumes of nitrous oxide diffuse outwards at the end of the anaesthesia when the patient is permitted to breathe air The oxygen in the inspired air is therefore diluted by the outward diffusion of nitrous oxide causing hypoxia and hypoxaemia This effect is very important to the anaesthetist

because hypoxaemia by this mechanism may occur not only at the end of an operation but during the anaesthetic when sucking out the trachea of the patient or when the anaesthetic machine is disconnected from the airway at any time. These

TABLE I

EFFECT OF CHRONIC PULMONARY DISEASE ON PULMONARY VENTILATION AND CARDIAC EFFICIENCY

CHRONIC PULMONARY DISEASE

↓

(1) Reduced ventilatory capacity of alveolar sacs
(2) Reduced circulatory capacity of vascular bed
(3) Reduced oxygen diffusing capacity
(4) Excessive dead space ventilation
(5) Excessive venous admixture

↙ ↘

Chronic hypercapnia	*Chronic hypoxia*
Pulmonary hypertension	Hypervolaemia
Hypertrophy and dilatation of right ventricle	Polycythaemia
Right ventricular failure —with low cardiac output if pulmonary fibrosis —with high cardiac output if pulmonary emphysema	Increased cardiac output

changes should be kept in mind, and prevented by the administration of 100 per cent oxygen prior to applying suction and prior to the changeover to breathing ambient air.

Pulmonary circulation

The pulmonary vascular system has a static blood volume of approximately 30 per cent (1300 millilitres) of the total blood volume and an arterial pressure of 25/8 millimetres of mercury. The pulmonary vascular bed is very distensible, and ordinarily an increase in cardiac output to three times normal will not increase pulmonary blood pressures. Further increases in blood flow, however, will increase the pressure rapidly. During normal inspiration of 500 millilitres of air, the blood content of the lung increases by 50 millilitres and the blood content of the thoracic veins by 100 millilitres. The pulmonary capillary bed has a pulsatile flow of 60 millilitres per second; that is, the capillary bed content approximates the stroke volume of the heart. Measurement of this blood flow is easily carried out by the acetylene or ethylene method of measuring cardiac output (Cournand, 1950b; Sjöstrand, 1953).

The importance of this circulation in the control of pulmonary ventilation has been increasingly appreciated during the past few years. The reasons are as follows: (1) Although the pulmonary vessels have no smooth muscle and are not constricted by drugs which constrict the peripheral vessels, it is now known that they have

vasomotor tone (2) Hypoxia or hypercarbia or both increase the pulmonary vascular resistance and pulmonary blood pressure These effects may cause reflex peripheral vasodilatation hypotension and tachypnoea or apnoea (3) The rapid injection of many drugs initiates cardiopulmonary reflexes often increasing pulmonary vascular constriction and causing apnoea (Aviado and Schmidt 1955)

Alveolar ventilation

After considering the numerous factors affecting the mechanical transfer of gas from the outside to the lung alveoli one must consider the ultimate factor in pulmonary ventilation namely the amount of gas which must come into contact with the very large alveolar surface (55 square metres) and the relatively small volume of blood flowing in the pulmonary capillary bed (about 60 millilitres per second) to ensure saturation of the blood with oxygen and removal of its carbon dioxide Estimation of the alveolar ventilation probably provides the clinician with the most valid indication of the effectiveness of the pulmonary ventilation by whatever means it is controlled The alveolar gas exchange per minute is calculated by dividing the millilitres of carbon dioxide exhaled per minute by its concentration For example an output of 200 millilitres per minute with a concentration of 5 per cent indicates an alveolar ventilation of 4 litres per minute

The excretion of carbon dioxide from the blood is a more convenient index of alveolar ventilation than is oxygen uptake since it is not affected so much by disturbances in distribution in the lung alveoli or by disturbances in diffusion across the pulmonary membrane Carbon dioxide diffuses across the membrane 25 times more rapidly than does oxygen, because of its greater solubility in body fluids

The alveolar ventilation depends on 3 main factors the rate of breathing, the depth of breathing (tidal volume) and the dead space in the respiratory tract It may be altered by three physiological factors the blood flow through the lungs (cardiac output), the *p*H of the blood, and changes in carbon dioxide production resulting from altered metabolism The level of alveolar ventilation is maintained by the respiratory centres which compensate for most changes in the lung The activity of the diaphragm and accessory muscles of respiration usually increases the total ventilation to overcome increased dead space decreased lung compliance, increased airway resistance and disturbances in distribution of gas and blood in the alveoli (Riley and Cournand 1949 1951 Suskind and Rahn 1954)

Ventilation nomogram—Radford Ferris and Kriete (1954) have integrated the major factors affecting alveolar ventilation into a nomogram on the basis of two predicted variables (1) the carbon dioxide production determined from established basal metabolism standards which take into account also the sex and body surface area and (2) the anatomical dead space which they arbitrarily set at the reasonable approximation of 1 millilitre per pound body weight

By aligning a rate of respiration with the patient s weight the basal tidal volume required to maintain a normal alveolar carbon dioxide tension is provided by the nomogram However the clinician who employs this aid must apply correction factors for deviations from the normal functional integrity of the lung which as has been seen may upset gaseous and blood distribution in the alveoli and may result in defective diffusion across the alveolo capillary membranes The clinician must also be prepared to estimate the effect of gross changes in cardiac output and

the metabolic acid base disturbances which may develop and to estimate a reason able correction factor for these

The anaesthetist must also evaluate the need for other correction factors (Orton 1952) An endotracheal tube eliminates about 50 per cent of the anatomical dead space whereas an anaesthetic face mask may add 100 per cent to the dead space controlled manual (or mechanical) ventilation increases the dead space by about 25 per cent ether anaesthesia may increase the dead space by as much as 50 per cent On the metabolic side ether anaesthesia raises the fixed acid content of the blood Each degree (F) rise of fever above 99° F increases carbon dioxide production by 10 per cent, so that alveolar ventilation must be correspondingly increased for each degree (F) rise in temperature Whether carbon dioxide production falls during hypothermia is not clear (Cranston Pepper and Ross 1955, Lohr and Ulmer, 1954) However pulmonary ventilation should be maintained at a normal rate until more information becomes available regarding the diverse and deleterious effects following the hypothermic state

The majority of patients with whom the anaesthetist must deal are not in the sitting position which is the best from the point of view of air resistance and compliance of the lungs Anaesthetized patients are also at a major disadvantage because their ability to compensate for increased resistance and decreased lung compliance is diminished by the state of anaesthesia It is therefore essential that assisted or controlled delivery of the estimated requirement for pulmonary ventilation should be provided particularly in the patient who is elderly, or who has cardiopulmonary disease (Attinger Monroe and Segal 1956)

The anaesthetist should also bear in mind the effect of premedication with belladonna derivatives and the possible effect of ganglionic blocking drugs These reduce bronchomotor tone and viscous resistance of the lung to the extent that dead space *may* increase 30 per cent or more The implication of belladonna drugs in this clinical effect has recently been questioned, and the apparent changes may actually have been due to ventilating the distensible tubing in the anaesthetic machine rather than any change in the dead space caused by bronchial dilatation Further work remains to be done to clarify this matter

Finally it is important that the rate of respiration selected should provide an alveolar ventilation which approximates 0 8 volumes of the pulmonary blood flow that is for a cardiac output of 5 litres per minute it is assumed that 4 litres per minute of alveolar ventilation is necessary Such a rate should also provide the maximum ventilation with the minimum work of breathing (Otis Fenn and Rahn 1950 McIlroy Marshall and Christie 1954)

Table II indicates a suitable rate and depth of breathing and some correction factors which are applicable to the patient under anaesthesia For example a 200 pound man who is to be ventilated at 18 respirations per minute with nitrous oxide and trichloroethylene anaesthesia in the supine horizontal position requires

475 millilitre = basal tidal volume
+ 180 millilitre = distensibility of anaesthetic circuit (hoses)
− 100 millilitre = decrease in dead space by endotracheal tube
+ 60 millilitre = increase in dead space by atropine

650 millilitre = approximate setting on a fixed volume ventilator

TABLE II

BASAL TIDAL VOLUMES (MILLILITRES) REQUIRED TO MAINTAIN ALVEOLAR VENTILATION OF NORMAL LUNGS

Correction factors apply to artificial pulmonary ventilation if patient has a paralysed respiratory control mechanism or if patient has received narcotics or is under general anaesthesia (*after Radford Ferris and Kriete 1954*)

RATE OF RESPIRATION (ADULT — CHILD — INFANT)	WEIGHT IN POUNDS: 6	15	30	50	75	100	125	150	175	200
50	15	35	65							
40	20	40	75	100	130	175				
30			85	110	150	200	250	300	325	375
25				140	175	225	275	325	350	400
20					200	250	300	350	400	450
18						275	325	375	425	475
16							350	400	450	525
14								450	500	575
12								525	575	650

+ Volume of distensibility of anaesthetic circuit

− 50 per cent of anat D S (endotracheal tube)

+30 per cent of anat D S for broncho dilatation (atropine)

+20 per cent for metabolic acidosis (ether)

+5 per cent for each degree of fever (above 99 F rectal)

+Mechanical dead space of mask

EFFECT OF ANAESTHETICS ON THE CONTROL OF PULMONARY VENTILATION

The effects of anaesthetics on the control of pulmonary ventilation have been measured in a number of ways of which three have been recognized as valid (1) a constant elevated arterial carbon dioxide tension is maintained and the change in pulmonary ventilation during anaesthesia is recorded, (2) a constant pulmonary ventilation is maintained by means of a pump in a curarized animal and the response to carbon dioxide before and after the administration of a drug is measured by action potentials in the phrenic nerve, and (3) a constant pulmonary ventilation during a steady level of anaesthesia is produced (a steady state) and the expired carbon dioxide as well as the arterial carbon dioxide tension and *p*H are measured Known concentrations of carbon dioxide are then added to the anaesthetic mixture and the changes in pulmonary ventilation, expired carbon dioxide, arterial carbon dioxide tension and *p*H are measured The last method appears to be the most reliable and valid (Dripps and Dumke 1943, von Euler and Sodenburg 1952 Lambertsen and his associates 1953 Eckenhoff and his colleagues 1955 Eckenhoff Helrich and Hege, 1956 Tenney 1956)

Four generic groups of drugs are used in anaesthetics namely hypnotics analgesics muscle relaxants and a variety of ancillary agents which are antihistaminic

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Effect on inflation and deflation receptors in the lung

The pulmonary stretch receptors are stimulated to varying degrees by all inhalation agents (Whitteridge and Bülbring 1944 1946 Whitteridge, 1950) This stimulation ceases when deep anaesthetic levels are reached Intravenous barbiturates (thiopentone) on the other hand cause a transient decrease in the response

The Hering Breuer inflation and deflation reflex is depressed by ether, cyclopropane and chloroform progressively as depth of anaesthesia is increased This may be secondary to depression of vagal afferent impulses to the medulla With thiopentone and morphine the reflex is exaggerated by the combined action of vagal afferent stimuli to the medulla, the hypoxic stimulus from the peripheral chemoreceptors and perhaps the release of endogenous serotonin

Nitrous oxide and ethylene do not depress or exaggerate this reflex in the absence of hypoxia Trichloroethylene and trifluoroethylvinyl ether cause rapid shallow breathing probably by stimulating the pulmonary deflation endings (Dundee 1957) Halothane (Fluothane) would appear to have a similar effect

Effect on musculoskeletal tone

The muscles primarily involved in pulmonary ventilation may be divided into two groups (1) Ordinary inspiration is supported by the diaphragm external intercostals intercartilaginae, levatores costarum scalenae and serratus posterior superior The contracting diaphragm produces about 75 per cent of the change in thoracic volume, and the other muscles cause increased tension between the ribs and the fixed bony parts of the thoracic cage Forceful inspiration depends on contraction of the sternocleidomastoids trapezei and pectoral muscles (2) Expiration during ordinary breathing depends on the normal recoil or relaxation of the inspiratory muscles and possibly contraction of the internal intercostals and triangularis sterni and forceful expiration depends on strong contraction of the anterior abdominal muscles (recti and obliques) serratus posterior inferior and quadratus lumborum

When the potent anaesthetics are used surgical anaesthesia causes progressive relaxation and paralysis of these muscles The more potent the agent the greater this effect This effect in the case of ether is not only central in origin but is due to interference with neuromuscular transmission In hypnotic doses the intravenous barbiturates do not alter muscle tone in the absence of hypoxia When a muscle relaxant is used in conjunction with hypnotic and analgesic drugs to produce balanced surgical anaesthesia, the muscles relax in direct proportion to the dose plus the effect of the anaesthetic administered with it

Effect on acid base homeostasis

A basic factor involved in acid base homeostasis is that the resting healthy adult utilizes 250 millilitres of oxygen and excretes a somewhat smaller volume of carbon dioxide each minute The most important function of pulmonary ventilation is to regulate exactly this exchange Under anaesthetic conditions alterations in this exchange influence to an important degree acid base homeostasis in the blood Such changes in turn affect many of the physicochemical and enzymatic reactions that regulate normal body function This aspect of blood chemistry forms

sympatholytic, parasympatholytic or which block nerve conduction Most of the drugs used have multiple actions, dependent upon the dose administered Each may upset the normal mechanisms for control of pulmonary ventilation The simplest way to summarize these effects is to consider their action from the brain centres, through the peripheral chemoreceptors, down to reflex and mechanical changes in the lungs (Watrous Davis and Anderson, 1950, 1951)

Effect on the brain centres

The dominant stimulus to pulmonary ventilation under anaesthesia is an elevation of the alveolar and arterial carbon dioxide tension Depression by anaesthetics is aggravated by hypoxia Even in the absence of hypoxia all anaesthetics (ether, cyclopropane, chloroform, trichloroethylene, thiopentone, and so on) and all analgesics (such as morphine, pethidine, and alphaprodine) depress the response of the centres to carbon dioxide Only nitrous oxide and ethylene seem to spare the centres in this regard However, the action of different agents on the centres varies so much that it is necessary to recognize the specific effect of each agent and to assist ventilation accordingly It is apparent to the clinician that those agents which cause the least irritation to the tracheobronchial tree induce the greatest central depression

Effect on peripheral chemoreceptors

The dominant stimulus to the carotid and aortic bodies during anaesthesia is a decrease in the oxygen tension of the arterial blood to levels below 70 millimetres of mercury The response of these receptors also varies with each anaesthetic agent With the intravenous barbiturates and narcotic analgesics an elevation in oxygen tension by oxygen administration may cause apnoea by removing the peripheral chemoreceptor stimulus (Beecher and Moyer, 1941), while deep ether cyclopropane and chloroform anaesthesia abolish this reflex by central depression or blockade of afferent vagal impulses Nitrous oxide ethylene and trichloro ethylene–nitrous oxide anaesthesia do not depress this reflex

Effect on tracheobronchial tree

The effect of anaesthetics on bronchomotor tone depends on whether the drug releases endogenous epinephrine acetylcholine, histamine or possibly serotonin Ether and chloroform cause dilatation due to increased epinephrine secretion vagal depression and smooth muscle paralysis whereas cyclopropane thiopentone and morphine cause varying degrees of constriction by vagal stimulation (Adriani and Rovenstine, 1943) The latter effect may be blocked effectively by atropine Nitrous oxide and ethylene do not affect the bronchi in the absence of hypoxia Antihistaminic drugs will cause bronchodilatation in subjects who have allergic bronchoconstriction

Parasympatholytic drugs (belladonna derivatives) sympathotonic drugs (ephedrine isoproterenol) and drugs causing smooth muscle relaxation (aminophylline) remove bronchomotor tone and thus cause dilatation of the bronchi Release of endogenous serotonin may be responsible for the tachycardia bronchoconstriction bucking and coughing seen with intravenous barbiturate anaesthesia (Spies and Stone, 1952, Ginzel and Kottegoda 1954)

curves Since for a given rise in carbon dioxide tension the increase of H_2CO_3 is relatively greater than that of $BHCO_3$ it follows that an excess carbon dioxide tension (hypoventilation) in the blood causes respiratory acidosis while a carbon dioxide tension deficit (hyperventilation) will result in respiratory alkalosis If the quantity of available alkali is reduced in the blood (fixed acid accumulation or loss of alkali) metabolic acidosis results whereas increased alkali in the blood (alkali ingestion or vomiting excess of acids) will cause metabolic alkalosis Adaptive processes in the body constantly strive to restore homeostasis when disturbances occur These are so finely adjusted that a few millimetres of mercury deviation of

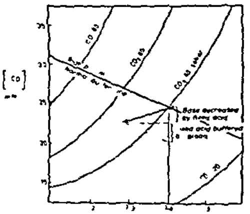


FIG 14—A 48 year-old male premedicated with 75 milligrams of pethidine and 0 6 milligrams of atropine With the patient in the supine horizontal position anaesthesia was maintained with ether and oxygen administered in a closed circuit system and sodalime absorption of carbon dioxide Respiration was spontaneous during 210 minutes of anaesthesia Initial arterial blood sample drawn *before* premedication $pH = 7\,42$ Total plasma carbon dioxide = 24 8 millimoles per litre Calculated carbon dioxide tension = 39 millimetres of mercury and plasma bicarbonate = 23 7 millimoles per litre Arterial blood sample at end of operation $pH = 7\,28$ Total plasma carbon dioxide = 24·0 millimoles per litre Calculated carbon dioxide tension = 50 millimetres of mercury and plasma bicarbonate = 22 5 millimoles per litre Fixed acid accumulation was relatively slight in this case

carbon dioxide tension in the arterial blood above or below 40 or a few units of change in the pH above or below 7 40 will ordinarily initiate a marked change in the pulmonary ventilation (Henderson 1928 Shock and Hastings 1934 1935 Gamble 1946 Davenport 1950) Anaesthetics suppress the adaptive processes and in many instances aggravate the disturbances

In Fig 14 a fundamental approach to the data necessary for the anaesthetist to understand acid base alterations in the arterial blood (the pH carbon dioxide tension and plasma bicarbonate concentration) is shown These 3 variables are related according to the following equation which is derived from the Henderson Hassebalch equation

$$pH = 6\,10 + \log \frac{(\text{Total carbon dioxide in plasma in millimoles per litre}) - (0\,03 \times \text{carbon dioxide tension in millimetres of mercury})}{0\,03 \times \text{carbon dioxide tension in millimetres of mercury}}$$

where the pK (6 10) is the constant for the bicarbonate buffer system at body temperature (37 C) which equals the product of the dissociation constant of carbonic acid (H_2CO_3) and the amount of dissolved carbon dioxide in the form of carbonic acid 0 03 is the factor for converting carbon dioxide tension in millimetres of mercury to carbon dioxide concentration in millimoles per litre and the numerator of the equation (the total carbon dioxide in plasma in millimoles per litre) − (0 03 × carbon dioxide tension) is equal to the plasma bicarbonate concentration in millimoles per litre $(HCO_3)_p$ The blood gas analyses as described above provide 2 of these factors—pH and total carbon dioxide in plasma in millimoles per litre The third is solved by substitution in the formula or derived from McLean s nomogram (McLean 1938)

the foundation of an understanding of the complex factors regulating acid base balance which are influenced by pulmonary ventilation and by anaesthetics

The study of alterations in acid base homeostasis induced by derangements in pulmonary ventilation due to anaesthetics has been a most difficult problem It is only little more than 5 years since technical advances have permitted continuous monitoring of ventilation during anaesthesia, and there is still no reliable way of indicating continuously the pH and carbon dioxide tension of the blood The best and most reliable answer still lies in the analysis of frequently drawn arterial blood samples even though such analyses are time consuming The analyses are not difficult to perform but are fraught with numerous sources of error which must be scrupulously controlled

The following is a brief outline of the essential techniques and data that must be obtained from blood samples to draw valid conclusions regarding acid base balance during anaesthesia the brachial artery is canalized pre operatively specially prepared 10 millilitre syringes which have been lightly coated with silicone or paraffin and contain a loose fitting metal washer or a small drop of mercury are employed for taking the blood the barrel of the syringe is rinsed with heparin and 0 2 millilitre is retained to fill the dead space of the connector to prevent the blood from clotting 10 millilitres of blood are drawn anaerobically before induction at intervals during anaesthesia and during the recovery period, after gentle mixing aliquots of these samples are used for analysis

The pH is measured immediately (within 20 minutes) or within 2 hours if the blood has been refrigerated The most reliable measurement of blood pH is obtained in a constant temperature pH microcell electrode set at the patient s body temperature Otherwise temperature corrections may be applied (Rosenthal, 1948) but these are only valid for blood in which haemoglobin content serum proteins and electrolytes are within normal limits The haematocrit is determined by centrifuging the blood in a Sanford Magath tube Oxygen capacity of the blood is determined directly according to Van Slyke and Sendroy s method (1928) From the corrected oxygen capacity the haemoglobin content is calculated Oxygen and carbon dioxide content of the whole blood and the total carbon dioxide content of the plasma are determined by a modification of the manometric method of Van Slyke and Neill (Van Slyke and Neill 1924 Goldstein and his colleagues 1950 Holaday and Verosky 1955) The modification is required to eliminate the influence of anaesthetic vapours in the blood The bicarbonate concentration in the plasma and the carbon dioxide tension may then be calculated from a formula derived from the Henderson Hassebalch equation (*see* below) or read off a nomogram based on the pH and the total carbon dioxide content of the plasma (McLean 1938 Singer and Hastings 1948) The oxygen saturation of the blood is calculated from the determined oxygen content of the blood (corrected for dissolved oxygen) and the corrected oxygen capacity

The physicochemical data are then expressed in terms of 3 variables in the blood the hydrogen ion concentration (cH) or more conveniently its negative logarithm to the base 10 (pH) the quantity of carbon dioxide in the form of free carbonic acid (H_2CO_3) and the bicarbonate concentration ($BHCO_3$)

The quantity of free carbonic acid is in direct proportion to the carbon dioxide tension, while the bicarbonate concentration at a given level of available alkali varies with the carbon dioxide tension in accordance with carbon dioxide absorption

number of such vectors are drawn in Fig 15 for several anaesthetic agents and methods The amount of fixed acid accumulation (that is acids other than carbonic acid which are not volatile and cannot be removed by the lungs) during administration of these anaesthetics may be calculated if the difference between the initial and final plasma bicarbonate concentration is corrected to *p*H 7 40 or may be determined by a simple construction on the graph as shown in Fig 14 a vertical line is drawn at *p*H 7 40 (through the intersection of the normal buffer line and the 44 millimetres of mercury carbon dioxide isobar) The initial point and the end point (arrowhead) are then projected parallel to the normal buffer line on to the vertical line The height of the projection indicates the excess amount of fixed acid in millimoles per litre which has accumulated during anaesthesia and includes the amount of acid which has been buffered by the blood The decrease in bicarbonate concentration is always less than the fixed acid accumulation (as appears on the graph) because of this buffering action of the blood and the difference may be determined by projecting the end point (arrowhead) on the *p*H 7 40 line The effects on acid base balance of ether, cyclopropane and the ultra short acting

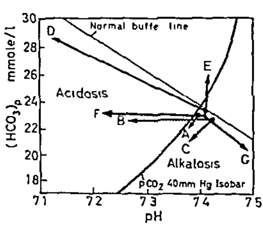


FIG 15—Effect of anaesthetics on pulmonary ventilation and acid base homeostasis A muscle relaxant nitrous oxide and oxygen and controlled pulmonary ventilation B ether nitrous oxide and oxygen and spontaneous breathing C ether nitrous oxide and oxygen and assisted breathing D cyclopropane oxygen and spontaneous breathing E cyclopropane oxygen and controlled pulmonary ventilation A E lines apply to closed system with carbon dioxide absorption F nitrous oxide and trichloroethylene administered through a Magill attachment (Mapleson A system) and controlled pulmonary ventilation G nitrous oxide and trichloroethylene administered through a non rebreathing system and controlled pulmonary ventilation

barbiturates (thiopentone hexobarbitone) have been discussed and studied in detail (Stehle and Bourne 1924, Dripps 1947 Beecher and Murphy, 1950 Dobkin and Van Bergen 1952 Brewster, Bunker and Beecher, 1952, Dundee, 1952 Weisberg 1953 Wilson, Hoseth and Dempsey, 1954 Lucas and Milne, 1955) If respiratory depressants are omitted in premedication, the following conclusions are valid

In light surgical planes of anaesthesia ether does not cause carbon dioxide accumulation during spontaneous respiration unless ventilation is impeded by abnormal postures splinting the diaphragm (packs retractors) or when a surgical pneumothorax is required A metabolic acidosis of moderate degree however is a regular accompaniment and is due to accumulation of lactic acid and serum inorganic phosphorus Cyclopropane and thiopentone cause carbon dioxide accumulation in proportion to the depression of the ventilation and can be effectively avoided in patients with normal lungs by adequate artificial ventilation (Dobkin and Van Bergen 1952) Trichloroethylene and trifluoroethylvinyl ether will cause hypoxia and hypercarbia due to inadequate alveolar ventilation if the tachypnoea produced by these two agents is allowed to persist (Dundee 1957) (Fig 15)

By plotting pH units as the abscissa and the bicarbonate concentration in millimoles per litre as ordinates of serial arterial (anaerobic) blood samples the physiological effects of altered pulmonary ventilation and anaesthetic drugs on acid base homeostasis become recognizable The value of such a graph is greatly enhanced by the addition of 2 kinds of guide lines

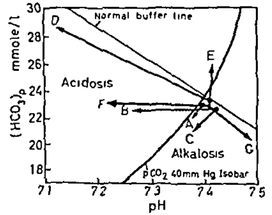
(1) *Carbon dioxide tension isobars* At any point on the graph where a line representing pH crosses a line representing bicarbonate concentration, there is a unique value of the carbon dioxide tension which satisfies the above equation Similarly, if the carbon dioxide tension and pH are determined a unique value for the bicarbonate concentration is found to satisfy the equation The locus of all points for a particular value of the carbon dioxide tension can therefore be found by substituting a range of values of pH and the particular carbon dioxide tension value in the equation and deriving the corresponding bicarbonate concentration By joining such a series of points the particular carbon dioxide tension isobar may be drawn on the pH bicarbonate graph A set of such isobars may be plotted on the graph when wide fluctuations in pH and carbon dioxide tension are expected

(2) *Normal buffer line* This line may be derived as follows Equilibrate several samples of normal human whole arterial blood (which is at body temperature and fully saturated with oxygen) in a series of gas mixtures containing known tensions of carbon dioxide The blood plasma is then removed from the erythrocytes under anaerobic conditions This is referred to as true plasma (If the plasma is separated without employing anaerobic conditions carbon dioxide is lost This is called separated plasma Since plasma alone is a very poor buffer of the blood the pH and bicarbonate content of separated plasma would not reflect the buffering power of the haemoglobin) The true plasma samples are analysed for total carbon dioxide content in millimoles per litre and for the percentage of carbon dioxide in the gaseous phase From the above determinations, the carbon dioxide tension of the gas (and therefore of the blood) and bicarbonate content and the pH of the plasma may be calculated For each true plasma sample the bicarbonate content and corresponding pH are plotted and joined by a line This is designated the normal buffer line This guide line is of importance in the pH bicarbonate graph because it indicates the degree of the buffering of fixed acids by the haemoglobin (Henderson 1928 Davenport 1950)

The ultimate significance of this graph lies in its lucid depiction of both the respiratory and metabolic alterations in acid base homeostasis which characteristically occur during anaesthesia Alterations in the blood which cause a shift to the left or right along the normal buffer line are due entirely to uncompensated alterations in pulmonary ventilation (acidosis and alkalosis respectively) and represent corresponding changes in the carbon dioxide tension Because of this the pH of the blood is altered A shift upwards or downwards on the carbon dioxide 40 millimetre of mercury isobar is due entirely to uncompensated alterations in the available buffer base as indicated by the plasma bicarbonate concentration (metabolic alkalosis or acidosis respectively) Similarly the pH of the blood is altered, but to a lesser degree Shifts during anaesthesia may of course occur in various directions, and the type of acidosis or alkalosis can be analysed according to the magnitude and direction of the shifts

If the pH and bicarbonate values for several blood samples (drawn before during and immediately after anaesthesia) are plotted on the graph described above the change in acid base balance due to the particular anaesthetic may then be indicated by the vector drawn to represent the magnitude and direction of the change A

number of such vectors are drawn in Fig 15 for several anaesthetic agents and methods The amount of fixed acid accumulation (that is acids other than carbonic acid which are not volatile and cannot be removed by the lungs) during administration of these anaesthetics may be calculated if the difference between the initial and final plasma bicarbonate concentration is corrected to *p*H 7 40 or may be determined by a simple construction on the graph as shown in Fig 14 a vertical line is drawn at *p*H 7 40 (through the intersection of the normal buffer line and the 44 millimetres of mercury carbon dioxide isobar) The initial point and the end point (arrowhead) are then projected parallel to the normal buffer line on to the *vertical line* The height of the projection indicates the excess amount of fixed acid in millimoles per litre which has accumulated during anaesthesia and includes the amount of acid which has been buffered by the blood The decrease in bicarbonate concentration is always less than the fixed acid accumulation (as appears on the graph) because of this buffering action of the blood and the difference may be *determined by projecting the end point (arrowhead) on the pH 7 40 line* The effects on acid base balance of ether, cyclopropane and the ultra short acting



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The effect of anaesthetic apparatus

The effect of anaesthetic apparatus on pulmonary ventilation is at present the subject of extensive investigation The following conclusions emerge from these studies

(a) *Carbon dioxide absorption in presently designed apparatus is inadequate for* clearance of the expired carbon dioxide when a closed system is employed due either to the quality of the absorbent material or to the design of the canisters Although enlarged canisters are now being advocated by some it is highly questionable whether it is the canister design that is at fault Other factors such as proper packing timed use and adequate assistance to respiration should be corrected first before the canisters now in use are discarded It seems clear that when a semi-closed system is employed adequate carbon dioxide clearance can be attained only by the use of a carbon dioxide absorption system and delivering at least the minute volume of the respiration required by the patient (Swartz Adriani and Mih 1953 Elam and Brown 1956 Bracken Lowe and Woolmer 1956 Lund Andersen and Erickson 1956 Nealon and his colleagues 1956)

(b) The resistance of anaesthetic apparatus and airway connexions at gas flow rates ordinarily employed in anaesthesia still requires reduction in order to eliminate the increased work of breathing imposed by the apparatus (Orkin Siegel and Rovenstine 1954 1957)

(c) The distensibility of the anaesthetic tubing has been overlooked by many When fixed volumes are delivered by a mechanical respirator as much as 300 millilitres may be taken up in an external circuit which does not employ semi rigid hoses Even with slight obstruction in the patient s airway between 100 and 200 millilitres of gas are lost in distending the external airways It is therefore essential either to compensate for this loss or to employ a rigid delivery system when the minute volume of respiration has been carefully determined as from a Radford nomogram reading (Dobkin and Wyant 1956)

Hypothermia

With the introduction of hypothermia into anaesthetic techniques a host of problems relating to acid base homeostasis and control of the pulmonary ventilation has arisen Acidosis which may prove fatal develops if ventilation is not vigorously supported at temperatures below 30 C due to depression of the hypoxic drive to the chemoreceptors Cold induces a change in the solubility of carbon dioxide in the blood the pH increases and the oxygen dissociation curve shifts to the left so that tissue hypoxia may result Thus a carbon dioxide tension of 40 millimetres is normal at 38° C, whereas 36 millimetres at 30 C and 33 5 millimetres at 25 C are normal (Fleming 1954 Brewin Nashat and Neil 1956) Opinions differ as to the value of adding carbon dioxide to the inspired air for the purpose of stimulating ventilation increasing the availability of oxygen to the tissues and preventing alkalosis during hypothermia It is felt that the relatively small increase in the pulmonary ventilation produced by adding carbon dioxide is not worth the extra burden of respiratory acidosis which is quickly accompanied by an increasing metabolic acidosis in the rewarming period

ARTIFICIAL CONTROL OF PULMONARY VENTILATION DURING ANAESTHESIA

Studies of controlled pulmonary ventilation have been carried out on dogs and humans under anaesthesia with closed and open chests in order to establish the respiration curve which is physiologically ideal on the basis of arterial oxygen

saturation oxygen tension carbon dioxide tension *pH* and blood pressure determinations and with which damage to the pulmonary parenchyma is avoided (Ankeney and his colleagues 1954 Waltz and his colleagues, 1954 Hubay and his colleagues 1954 Dobkin and his colleagues, 1956 Gordon Frye and Langston, 1956) It was found that the pressure curve should have a gradual rise to a short inspiratory plateau followed by an abrupt expiratory fall to a longer expiratory plateau, which must reach atmospheric pressure during the last third of the cycle Adverse effects of intermittent positive pressure respiration previously reported were due undoubtedly to one of two possibilities either mechanical respiratory devices did not return the pressure to zero (atmospheric pressure) during the expiration phase or the duration of the expiration phase was too short (Price Conner and Dripps 1954)

These studies showed that positive-negative pressure (PNP) inflation could provide better controlled ventilation in the closed chest, because the low mean airway pressure thus achieved avoids the deleterious effects of the inspiratory positive pressure on cardiac refill, cardiac output and arterial blood pressure (Thompson 1948 Maloney and his colleagues, 1953) When the chest was open however no benefit was found with the PNP In fact when PNP was excessive, ventilation was depressed due to trapping PNP was recommended for open chest work with a small negative pressure phase (−5 millimetres of mercury) in emphysematous or other patients only if visible deflation of the lung was unsatisfactory When there is extrinsic expiratory resistance due to a narrow endotracheal tube the negative expiratory phase may prevent over distension of the lung A rapid cycling rate does not allow sufficient time for adequate deflation without a negative phase and over distension from any cause may hinder the surgeon and necessitate negative pressure deflation to reduce the obscuring of the operative field However, excessive negative pressure promotes lung collapse which then requires excessive pressure to reinflate Such collapse produces an effective arteriovenous shunt (Dobkin and Wyant, 1956)

An intermittent positive pressure (IPP) amplitude of approximately 15 millimetres of mercury usually provides uniform and adequate alveolar ventilation Pressure volume studies indicate that slightly more pressure is usually required for adequate re inflation in the open chest than in the closed chest due to changes of surface tension within the lung alveoli, greater mobility of the bronchioles, and changes in visco elastic properties of the lung parenchyma

Dobkin and his colleagues (1956) and Gordon Frye and Langston (1956) found that for both IPP and PNP in the open or closed chest, an inspiration expiration time ratio of 1 2 provided optimal ventilation and the least deleterious effect on the circulation The range of pressures in millimetres of mercury which they found most satisfactory was plus 15 to minus 5 (PNP) and plus 15 to 0 (IPP) Considering operating conditions Dobkin and Wyant (1956) found that the use of positive, atmospheric and negative phases (PAN) in 1 1 1 ratio was most satisfactory using pressures of plus 15 0 minus 5 They found that although ventilation was usually satisfactory with PNP and IPP using the above pressures operating conditions were not so good as with PAN On the other hand Allbritten Haupt and Amadeo (1954) reported satisfactory operating conditions with the duration of the inspiratory phase twice that of expiration while Nealon and his colleagues (1956) found conditions best when the two phases were equal

In deciding on the ideal rate of artificial respiration for an individual patient three factors must be considered in this order (1) the alveolar ventilation required, (2) the physiological dead space, and (3) the degree of diaphragm motion and lung motion which can be tolerated by the surgeon The slower the rate employed the greater will be each of these factors The rate must, therefore, be adjusted for the optimal alveolar ventilation without increasing the other two factors

The rate found to be most satisfactory for pulmonary ventilation and operating conditions by Dobkin and his colleagues (1956) was 18 per minute, whereas Gordon Frye and Langston (1956) found that 12 per minute was adequate These two are within the most satisfactory range At the slower rate, however, the physiological ideal may be missed if surgical pneumothorax is present, because adequate alveolar ventilation is difficult to attain without vigorous flushing of the alveolar spaces especially when extensive pulmonary disease is present as is usual during pulmonary surgery As Gordon Frye and Langston (1956) have stated so clearly adequate alveolar ventilation depends primarily on adequate flushing of the alveolar gas and not necessarily on sucking out the alveolar gas with negative pressure

It is evident to the clinician that any system of artificially controlled respiration which assumes that each patient who is subjected to a fixed amplitude of airway pressure change will be provided with the same degree of pulmonary ventilation is relying on a misconception The distensibility of the air passages and lungs and the resistance of the airway system are rarely uniform from patient to patient Similarly any system which provides a fixed volume of ventilation based on calculated requirements of the patient may convey a false sense of security The efficiency of the carriage of oxygen by the blood depends on normal circulation through the lung with a minimum of arteriovenous shunting on a normal circulating blood volume and haemoglobin on the absence of lung air trapping due to emphysema and bronchitis, on the absence of pathological conditions of the pulmonary alveolar membrane caused by oedema or fibrosis and on the unimpeded output of carbon dioxide and the uptake of oxygen All these might be enzymatically or chemically disturbed by the anaesthetic drugs or by reactions to stress imposed by the operative procedure

PULMONARY FUNCTION TESTS

For the anaesthetist studies of pulmonary function must be diagnostic and prognostic in order to have clinical value (Christie and Bates 1955 Dayman 1956 Bates Knott and Christie 1956) As with liver and kidney function several tests are required in order that a recognizable pattern of dysfunction can be distinguished These tests should be designed to help the anaesthetist to decide on the most satisfactory pressure–volume contour for pulmonary ventilation to help the surgeon localize diseased and healthy lung parenchyma and to decide how much diseased lung tissue may be removed without leaving the patient a respiratory cripple or with insufficient functioning tissue compatible with life The trend at present is to find a few simple tests which are of highly significant value However, the anaesthetist must still strive to find simple means for monitoring continuously pulmonary ventilation during anaesthesia and recording alveolar carbon dioxide tension oxygen tension and *p*H in the arterial blood in order that valid adjustments can be made during the course of an anaesthetic

CONCLUSION

If the various factors which have been reviewed are considered, one can see immediately that there are numerous unknowns and variables continuously affecting the patient's voluntary and involuntary control of pulmonary ventilation while under the stress of disease and anticipated operation, and to these must be added the stress of the anaesthetic drugs and operative trauma

Anaesthetists must therefore, increase the efficiency with which they apply pulmonary ventilation by learning more about and improving (1) carbon dioxide absorption systems in anaesthesia, (2) resistance and distensibility (elasticity) of the delivery tubes in anaesthetic circuits (3) the changes (if any) in elasticity of pulmonary tissue during employment of various anaesthetic techniques and drugs (4) the mechanics of pulmonary ventilation, and (5) by developing tests which will help the anaesthetist to predict and observe the responses of the patient to anaesthetics and to the altered circulatory and ventilatory dynamics during operation

Many features of the control of pulmonary ventilation remain dark and mysterious regions in our rapidly expanding knowledge of human physiology The anaesthetist and the clinical physiologist must continue, therefore, to seek the simplest means of procuring further data to enable compensation for elements not perceived by the senses

REFERENCES

Adriani J and Rovenstine E A (1943) *Anesthesiology* 4 253
Allbritten F F Jr Haupt G J and Amadeo J H (1954) *Ann Surg* 140 569
Ankeney J L Hubay C A Hackett P R and Hingson R A (1954) *Surg Gynec Obstet* 98 600
Arnott W N (1955) *Brit med J* 2 279 342
Asmussen E and Nielsen M (1949) *Acta physiol scand* 20 79
Astrom A (1952) *Acta physiol scand* 27 *Suppl* 98
Attinger E O Herschfus J A and Segal M S (1956) *J clin Invest* 35 912
— Monroe R G and Segal M S (1956) *J clin Invest* 35 904
Aviado D M Jr and Schmidt C F (1955) *Physiol Rev* 35 247
Baldwin E de F Cournand A and Richards D W Jr (1949) *Medicine* 28 201
Banus M G Corman H H Perlo V P and Poplin G L (1944) *Amer J Physiol* 142 121
Bates D V (1956) *Pulmonary Circulation and Respiratory Function* A Symposium Dundee Queen's College
— Knott J M S and Christie R V (1956) *Quart J Med* 25 137
Baxter D W and Olszewski J (1955) *J Neurophysiol* 18 276
Bean J W and Johnson P C (1955) *Amer J Physiol* 180 438
Beecher H K and Moyer C A (1941) *J clin Invest*, 20 549
— and Murphy A J (1950) *J thorac Surg* 19 50
Bjurstedt A G H (1946) *Acta physiol scand* 11 *Suppl* 38
Bracken A de C Lowe S G and Woolmer R (1956) *Proc R Soc Med* 49 215
Brewin E G Nashat F S and Neil E (1956) *Brit J Anaesth* 28 1
Brewster W R Jr Bunker J P and Beecher H K (1952) *Amer J Physiol* 171 37
Brown E B Jr (1953) *Physiol Rev* 33 445
Buckley J J Van Bergen F H Dobkin A B Brown E B Jr Miller F A and Varco R L (1953) *Anesthesiology* 14 226
Christensen H (1954) The Chemical and Nervous Control of Respiration *Handbook of Respiratory Physiology U S A F School of Aviation Medicine* Ed Walter M Boothby Published as project no 21-2301-0003 of the U S A F School of Aviation Medicine
Christie R V (1953) *Proc R Soc Med* 46 381
— and McIntosh C A (1934) *J clin Invest* 13 299
— and Bates D V (1955) *Annu Rev Med* 6 211

Clausen J (1951) *Acta Psychiat Kbh* 74 *Suppl* 68
Comroe J H Jr (1953) *Harvey Lect* 48 110
— and Dripps R D (1946) *J Amer med Ass* 130 381
— — (1950) *The Physiological Basis for Oxygen Therapy* Springfield Thomas
— Forster R E Dubois A B Briscoe W A and Carlsen E (1955) *The Lung* Chicago Year Book Publishers
Cournand A (1950a) *Circulation* 2 641
— (1950b) *Harvey Lect* 46 68
— Motley H L Werko L and Richards D W Jr (1948) *Amer J Physiol* 152 162
— Richards D W Jr Bader R A Bader M E and Fishman A P (1954) *Trans Ass Amer Phys* 67 162
Cranston W I Pepper M C and Ross D N (1955) *J Physiol* 127 380
Daly M D B Lambertsen C J and Schweitzer A (1953) *J Physiol* 119 292
— — — (1954) *Ibid* 125 67
Davenport H W (1950) *The ABC of Acid Base Chemistry* 3rd Ed Chicago University of Chicago Press
Davies C E and MacKinnon J (1949) *Lancet* 2 883
Dawes G S and Comroe J H (1954) *Physiol Rev* 34 167
Dayman H G (1951) *J clin Invest* 30 1175
— (1956) *N Y St J Med* 56 2813
De Castro F (1951) *Acta physiol scand* 22 14
Dobkin A B (1958) *Canad Anaesth Soc J* In press
— and Van Bergen F H (1952) *Bull Univ Minn Hosp* 23 410
— and Wyant G M (1956) *Brit J Anaesth* 28 353
— Hubay C A Mendelsohn H and Hingson R A (1956) *Brit J Anaesth* 28 296
Draper W B Whitehead R W and Spencer J H (1947) *Anesthesiology* 8 524
Dripps R D (1947) *Anesthesiology* 8 15
— and Dumke P R (1943) *J Pharmacol* 77 290
— and Severinghaus J W (1955) *Physiol Rev* 35 741
Dundee J W (1952) *Brit med J* 2 893
— (1957) *Proc R Soc Med* 50 191
Eckenhoff J E Helrich M and Hege M J D (1956) *Anesthesiology* 17 66
— — — and Jones R E (1955) *J Pharmacol* 133 332
Elam J O and Brown E S (1956) *Anesthesiology* 17 116 128
Euler C von and Sodenburg V (1952) *J Physiol* 118 545 555
— Liljestrand, G and Zotterman Y (1939) *Arch physiol scand* 83 132
Fink B R (1955) *Anesthesiology* 16 511
Fleming R (1954) *Arch Surg* 68 145
Flourens M (1842) *Recherches experimentales sur la proprietes etc du systeme nerveux* 2nd ed Paris Bailliere
Fowler W S (1952) *Physiol Rev* 32 1
Franklin W Micholson A L Lowell F C and Schiller I W (1955) *New Engl J Med* 253 799
Fry D L Ebert R V Stead W W and Brown C C (1954) *Amer J Med* 16 80
Gamble J L (1946) *Chemical Anatomy Physiology and pathology of extra cellular fluid* 5th Ed Cambridge Harvard University Press
Gesell R Lapides J and Levin M (1940) *Amer J Physiol* 130 155
Ginzel K H and Kottegoda, S R (1954) *J Physiol* 123 277
Goldensohn E S (1955) *Psychosom Med* 17 377
Goldstein F Gibbon J H Jr Allbritten F F Jr and Stayman J W Jr (1950) *J biol Chem* 182 815
Gordon, A S Frye C W and Langston H T (1956) *J thorac Surg* 32 431
Gray J S (1949) *Pulmonary Ventilation and Its Physiological Regulation* Springfield Thomas
— Grodins F S and Carter E T (1956) *J appl Physiol* 9 307
Hall M (1836) *Lectures on the Nervous System and Its Diseases* Philadelphia Carey and Hart
Haldane J S and Priestley J G (1905) *J Physiol* 32 225
Henderson L J (1928) *Blood A Study in General Physiology* New Haven Yale University Press
Hering E and Breuer J S B (1868) *Akad Wiss Wien* 57 672

Hering E and Breuer J S B (1868) *Akad Wiss Wien* 58 909
Hesser C M (1949) *Acta physiol scand* 18 *Suppl* 64
Heymans C (1955) *Pharmacol Rev* 7 119
— De Vleeschhouwer G R (1956) *Amer Rev Physiol* 18 387
Hoff H E and Breckenridge C G (1954) *Arch Neurol Psychiat* 72 11
Holaday D A and Verosky M (1955) *J Lab clin Med* 45 149
Hubay C A Waltz R C Brecher G A Praglin J and Hingson R A (1954) *Anesthesiology* 15 445
Jones D S Beargie R J and Pauly J E (1953) *Anat Record* 117, 17
Kerr D I B Dunlop C W Best E D and Mullner J A (1954) *Amer J Physiol* 176 508
Krogh M (1915) *J Physiol* 49 271
Lambertsen C J Kough R H Cooper D Y Emmel G L Loeschke H H and Schmidt C F (1953) *J appl Physiol* 5 803
Legallois C (1812) *Experiences sur le Principe de la Vie* Paris D Hautel
Liljestrand A (1953) *Acta physiol scand* 29 suppl 106
Lilienthal J L Jr and Riley R L (1954) *Annu Rev Med* 5 237
— Riley R L Proemmel D D and Franke R E (1946) *Amer J Physiol* 147 199
Lohr B and Ulmer W (1954) *Arch klin Chir* 279 793
Low F N (1952) *Anat Rec* 113 437
Lucas B G B and Milne E H (1955) *Thorax* 10 354
Lucas D S (1955) *Med Clin N Amer* 39 661
Lund I Andersen K L and Erickson H (1956) *Brit J Anaesth* 28 13
Maloney J V Elam J O Hanford S W Balla G A Eastwood D W Brown E S and Ten Pas R H (1953) *J Amer med Ass* 152 212
McIlroy M B and Eldridge F L (1956) *Clin Sci* 15 329
— Marshall R (1956) *Ibid* 15 345
— — Christie R V (1954) *Ibid* 13 127 137 147
— Eldridge F L and Stone R W (1956) *Ibid* 15 353
— Mead J Selverstone N J and Radford E P (1955) *J appl Physiol* 7 485
— Eldridge F L Thomas J P and Christie R V (1956) *Clin Sci* 15 337
McLean F C (1938) *Physiol Rev* 18 495
Mead J and Whittenberger J L (1953) *J appl Physiol* 5 779
Meduna L T (1950) *Carbon Dioxide Therapy A Neurophysiological Treatment of Nervous Disorders* Springfield Thomas
Nealon T F Haupt G J Price J E and Gibbon J H Jr (1955) *J thorac Surg* 30 665
— — Chase H F Price J E and Gibbon J H Jr (1956) *J thorac Surg* 32 464
Nielsen M and Smith H (1951) *Acta physiol scand* 24 293
Orkin L R Siegel M and Rovenstine E A (1954) *Curr Res Anesth* 33 217
— — — (1957) *Ibid* 36 19
Orton R H (1952) *Anaesthesia* 7 211
Otis A B (1954) *Physiol Rev* 34 449
— Fenn W O and Rahn H (1950) *J appl Physiol* 2 592
— McKerrow C B Bartlett R A Mead J McIlroy M B Selverstone N J and Radford E P (1956) *J appl Physiol* 8 427
Pask E A (1955a) *Proc R Soc Med* 48 239
— (1955b) *Lancet* 1 1330
Perkins J F Jr Adams W E Flores A (1956) *J appl Physiol* 8 455
Pitts R F (1946) *Physiol Rev* 26 609
— (1949) In Fulton J F *Textbook of Physiology* 16th ed Philadelphia Saunders
— Magoun H W and Ranson S W (1939) *Amer J Physiol* 126 673 689 127 654
Price H L Conner E H and Dripps R D (1954) *J appl Physiol* 6 517
Prinzmetal M and Kountz W B (1935) *Medicine* 14 457
Radford E P Ferris B G and Kriete B C (1954) *New Engl J Med* 251 877
Rahn H and Otis A B (1949) *Amer J Physiol* 157 445
— Sadoul P Farhi L E Shapiro J (1956) *J appl Physiol* 8 417
Riley R L (1954) *Ann intern Med* 41 172
— and Cournand A (1949) *J appl Physiol* 1 825
— — (1951) *Ibid* 4 77

Riley R L Cournand A and Donald K W (1951) *Ann intern Med* 4 102
Rodbard S (1953) *Amer J Med* 15 356
Rosenthal T B (1948) *J biol Chem* 173 25
Rossier P H and Buhlman A (1955) *Physiol Rev* 35 860
Schmidt C F and Comroe J H (1940) *Physiol Rev* 20 115
Severinghaus J W and Stupfel M (1955) *J appl Physiol* 8 81
Shock N W and Hastings A B (1934) *J biol Chem* 104 585
— — (1935) *Ibid* 112 239
Singer R B and Hastings A B (1948) *Medicine*, 27 223
Sjostrand T (1953) *Physiol Rev* 33 202
Spalding J M K (1955) *Lancet* I 1099
Spies T D and Stone R E (1952) *J Amer med Ass* 150 1599
Stehle R L and Bourne W (1924) *J biol Chem* 60 17
Suskind M and Rahn H (1954) *J appl Physiol* 7 59
Swartz C H Adriani J and Mih A (1953) *Anesthesiology* 14 437
Tenney S M (1956) *Anesthesiology* 17 82
Thompson S A (1948) *J thorac Surg* 17 323
Van Slyke D D and Neill J M (1924) *J biol Chem* 61 523
— and Sendroy J Jr (1928) *Ibid* 79 781
Wade O L (1954) *J Physiol* 124 193
Waltz, R C Hubay C A Ankeney J L and Merrill J (1954) *Surg Gynec Obstet* 99 580
Watrous W G Davis F E and Anderson B M (1950) *Anesthesiology* 11 538 661
— — — (1951) *Ibid* 12 33
Weisberg H F (1953) *Amer J clin Path* 23 1082
Whitfield A G W Waterhouse J A H and Arnott W M (1950) *Brit J soc Med* 4 1 86 and 113
Whitteridge D (1950) *Physiol Rev* 30 475
— and Bulbring E (1944) *J Pharmacol* 81 340
— — (1946) *Brit med Bull* 4 85
Wilson R H Hoseth W and Dempsey M E (1954) *Amer J Med* 17 464
Wu N Miller W F and Luhn N R (1956) *Anesthesiology* 17 696

CHAPTER 8

SURGICAL TRAUMA—ANAESTHESIA AND THE CIRCULATION

R P Harbord

The modern trend in anaesthesia is to obtain a precise knowledge of function in relation to the use of agents and techniques, and this applies particularly to circulatory disorders Unlike accidental injury, surgical injury is a respector of parts and persons and although the disorders differ quantitatively they correspond qualitatively Amputation through the thigh, carried out before the advent of anaesthesia had a mortality of not less than 60–70 per cent the introduction of anaesthetics resulted in a saving of 11–20 lives for every 100 operations of this kind (Gordon 1897) The mechanism by which anaesthesia effected so dramatic a change has never been precisely revealed, although it is clear that the surgeon had more time he could therefore deal more adequately with haemorrhage

The changes due to anaesthesia are difficult to assess, because many other factors are at work during surgical operations and the individual agents and techniques of administration each have their own distinct effects The assessment of the pure effects of mechanical injury is also difficult as injury and haemorrhage are often combined in one patient The main illness arising from injury is compounded of (1) metabolic disturbances, (2) fluid distribution alterations and (3) nervous disorders

The nervous reaction to injury can be so trivial as to pass almost unrecognized or it may end in sudden death and for this the offending stimulus may be no more than the prick of a needle The circulatory disorders which are so prominent a feature soon after severe injuries most probably have their origin in good measure from changes in fluid distribution It may be that toxic factors contribute to the illness or that substances normally present in the body produce disturbance from an unusually high concentration

Many problems have been investigated in animals but the results *cannot* necessarily be applied to man, in whom clear evidence is harder to gain, nevertheless much is now being learnt directly from man as perfection is achieved in the techniques of observation and in the design of experiments which do no harm

PART 1 SURGICAL TRAUMA

METABOLIC DISTURBANCES AFTER INJURY

Depletive responses

After limb fracture injuries in man nitrogen sulphur and phosphorus are lost (Cuthbertson 1929 and 1930) Normal volunteers in splints and confined to

bed had small losses in comparison with fracture patients Disuse atrophy was not considered the origin of the negative nitrogen balance, and anaesthesia is probably not related because in Cuthbertson s series the patient who had the greatest loss of nitrogen had no anaesthetic The nitrogen loss was most marked between the fourth and eighth day after accident, but the peak occurred earlier in patients after surgical injury (osteotomy) By 10 days approximately 8 per cent of body weight of nitrogen had been lost this amounts to more than the nitrogen content of the entire liver Nitrogen loss persists, though in less degree for as long as 6 weeks after injury

According to Engel (1952), there is a fall in the amino acids in plasma which can be detected within 1 hour of injury and before the negative nitrogen balance Adrenaline insulin and growth hormone are all capable of producing a similar change but its significance after injury is not known The change is unlikely to be due to the influence of the endocrine glands because it occurs in hypophysectomized, adrenalectomized and adrenomedullated animals It will also occur in the demedullated animal

It appears that there is a generalized katabolic disturbance (Cuthbertson 1954), and tachycardia, pyrexia and an increased oxygen consumption accompany it It is not possible to prevent the katabolic process by giving a high protein diet to injured patients Howard and his colleagues (1946) found excessive losses of potassium after fracture injuries which were maximal in the first 24 hours The loss of nitrogen is not confined to fracture injuries, for Wilkinson and his colleagues (1950) found a loss of potassium and phosphorus, preceding losses of nitrogen and sulphur, after gastrectomy operations

Retention responses

Certain substances are however, retained after injury Sodium excretion was found to be decreased for 2–5 days according to Moore and Ball (1952) With massive injuries they found a fall of sodium in the plasma at the time of the positive sodium balance Browne (1945) found practically no excretion of ascorbic acid until 21 days after fracture injuries, despite a daily intake of up to 700 milligrams in orange juice

Hormone changes after injury

There is abundant evidence indicating that changes occur in the glands of internal secretion after injury Moore and Ball (1952) found a fall in the circulating eosinophil cells after injury and an increase in steroid hormones which suggested activity in the pituitary gland and adrenal cortex In considering the retention of ascorbic acid Kark and his colleagues (1952) showed that its consumption by the adrenal gland for cortical hormone synthesis could not be marked in man Their work indicated that adrenocortical activity is not the cause for ascorbic acid consumption after injury

Additional information has come from animal experiments Ingle, Ward and Kuizenga (1947) compared the extent of urinary non protein nitrogen after fracture injuries in normal rats and in rats maintained by saline solution after adrenalectomy Nitrogen excretion was increased in normal rats but there was no change in the other group A further comparison was made between normal rats and adrenalectomized rats which were maintained on a constant dosage of cortical

hormone In this case the injuries produced an identical response Since a constant dose of cortical hormone was given the increase in nitrogen excretion could not be attributed to hypersecretion of adrenal hormone Ingle, Meeks and Thomas (1951) demonstrated a similar relationship in the case of sodium chloride retention after injury Although cortical hormone is not secreted in excess, nevertheless it appears to be related to these changes

According to Cuthbertson (1954) a crude extract obtained from the anterior part of the pituitary gland is capable of eliminating the negative nitrogen balance in rats and Eliel Pearson and White (1952) have been able to produce a loss of nitrogen, phosphorus and potassium—similar to that which occurs after injury—by the administration of cortisone and ACTH to patients De Groot and Harris (1950) working on rabbits and Hume and Wittenstein (1950) using dogs, have independently shown that an intact hypothalamus is essential for ACTH release after stress The work of McCann (1953) suggests that injury stimulates the hypothalamus either by nervous or chemical (adrenaline) influences to produce ACTH release Furthermore, Porter (1952) has been able to detect electrical changes in the hypothalamus during conditions of stress

Other changes after injury

There are also disorders in carbohydrate metabolism (Engel 1952) which are in the nature of an impairment of carbohydrate utilization The rise in blood sugar occurring soon after injury is probably due to adrenal medullary secretion There is also a tendency for the development of fatty changes in the liver and for ketosis Morphological changes have been observed in lymphoid tissue and there is an eosinopenia Other endocrine changes are ascorbic acid and cholesterol depletion of the adrenal cortex and an increase in the corticoid content of the blood and urine Some of these changes have been observed with overdoses of adrenocortical hormone and this has led to the supposition that they all result from adrenal hypersecretion in response to injury They may be related to adrenal function but the work of Ingle, Ward and Kuijenga (1947) demonstrated that they are not all due to excessive adrenal secretion

Significance of metabolic changes

The precise significance of the metabolic disorders after injury is not clear Cuthbertson (1954) suggested that the negative nitrogen balance is in some way bound up with reparative processes Engel (1952) wondered whether some of the changes are due to reduced blood flow through individual organs Heinermann Smythe and Marks (1953) bled dogs in amounts up to 1 3 per cent to 3 9 per cent of body weight No attempt was made to standardize the extent of the hypoten[illegible] produced by the haemorrhage and the loss in these experiments did not nece[illegible] result in any significant fall in blood pressure They found that the blood f[illegible] through the liver decreased to 40 to 81 per cent of the control [illegible] haemorrhage The renal blood flow also became markedly reduced at th[illegible] Within 23–70 minutes there was a spontaneous recovery of the [illegible] blood flows towards normal Since the blood pressure change [illegible] probable that the diminished blood flows were due to va[illegible] metabolic changes may be related to this state On the other [illegible]

an intrinsic change in the organ interferes in some way with the metabolism of certain substances passing through it

Whatever may be the precise significance of these changes the anaesthetist should anticipate that a patient may react abnormally during the period after injury when the disorders are most marked Deep anaesthesia with toxic agents would be contra indicated in these circumstances

CHANGES IN THE DISTRIBUTION OF FLUID AFTER INJURY

Local changes at the site of injury

Cannon and Bayliss (1919) believed that the circulatory changes occurring after injury were due to a toxic metabolite set free from damaged muscle Others thought that the circulatory failure might be due to loss of fluid from the site of injury

Blalock (1931) was able to produce limb injuries in dogs in which the extravasated fluid amounted to about 4 or 5 per cent of body weight He compared the fall in blood pressure occurring with these injuries with the fall in blood pressure after repeated haemorrhages, controlled so that the amount of blood loss was similar, and took place over a similar interval of time His results suggested that the amount of blood lost in the extravasation was sufficient to cause the circulatory disorder

Courtice (1946), using rabbits, was able to produce extravasations with a marked fall in blood pressure from thermal injuries below the knees He found that the volume of blood lost was greater than the original plasma volume By keeping the injured limb cold immediately after scalding, he decreased the rate of fluid loss and prevented circulatory failure When the fluid loss was greatly decreased by the use of pressure bandages, the mortality was correspondingly reduced Other workers—Cameron and his colleagues (1945), Swingle and his colleagues (1942) and Duncan and Blalock (1942)—have also made similar observations

Courtice (1954) reviewed the events after injury and stressed that the first disturbance results in a loss of blood from ruptured vessels and, in addition a protein rich fluid accumulates This is due to an alteration of the permeability of the capillaries in the *injured* region Thus a local swelling is produced The protein rich fluid is re absorbed into the circulation by the lymphatic channels draining the area this process being speeded up by the pressure of the swelling or slowed when the blood clots

General disturbances

The main compensatory shift of fluid after injury is from the *uninjured* tissues so that a non protein fluid passes from the extravascular into the intravascular compartment If the subject is dehydrated before injury there may not be sufficient fluid to replace the intravascular loss and the general condition is likely to deteriorate more rapidly than otherwise

The cell membrane separates the body water which is about 71 per cent of the subject's weight (McCance and Widdowson 1951) into the intracellular and extra cellular phases which have a differing electrolyte pattern (Gamble, 1952) the

intracellular phase containing most of the potassium, and the extracellular phase most of the sodium in the body Skin and muscle are the tissues which occur in the greatest bulk and a high proportion of the extracellular water is in the skin, whereas most of the intracellular water is in the muscle (Courtice, 1954) When water is required for the preservation of the organism it is drawn from these two sources, so that the skin becomes dehydrated and the muscle wastes (Cameron and Courtice 1948) When fluid is required to replace the intravascular compartment over a prolonged period, then water is lost from the cells, chiefly the muscles (Elkington and Winkler 1944) Loss of weight and a release of potassium and nitrogen then take place

The permeability of the capillaries generally

The permeability of the capillaries in the uninjured area through which water passes into the vascular compartment to make good the loss from injury, has been studied by many workers Circulatory failure could, in theory, result from an altered permeability (Moon and his colleagues, 1941) as well as from the liberation of a toxic substance Courtice and Korner (1952) concluded that the permeability of the lung capillaries to protein was not altered in rabbits breathing 10 per cent oxygen although Landis (1928) had previously shown that severe anoxia can affect the capillary permeability to proteins Gibson and his colleagues (1947), using radioactive tracers, were able to show that no generalized increase in capillary permeability occurred after most types of injury No toxic factor has yet been isolated which is released in sufficient amounts after injury to affect the permeability of the capillaries in the uninjured vessels

Compensatory actions of the kidneys and pituitary gland

After a severe injury less urine is secreted This may be partly due to the reduced blood pressure or to vasoconstriction in the kidney There is also an increased concentration of the antidiuretic hormone from the posterior pituitary gland Le Quesne and Lewis (1953) suggested that the gland is affected more by emotion and afferent impulses from the injured area than from a rise in the osmotic pressure of the plasma Moore (1953) has shown that with surgical injury there is a retention of water and sodium as well as other indications of increased activity of the adrenal cortex These actions tend to maintain the blood volume

EFFECTS OF INJURY ON THE CIRCULATION

General effects

Zweifach (1951) gave values of cardiovascular function commonly found in studies after injury as follows the blood pressure falling to the region of 50 millimetres of mercury the rise in heart rate to over 200 per minute the fall in cardiac output from 2 5 to 0 4 litres per minute (Fick method), the reduction of blood volume to 65 per cent of normal the red cell haematocrit reduction to 30 per cent, the increase of peripheral resistance from 1,200 to 1,500 dynes per second per square centimetre due to peripheral vasoconstriction

Effects on the heart

A syndrome resembling that found after haemorrhage occurs with coronary thrombosis and it may be that cardiac function is altered after injury Bing (1952)

postulated that a reduction in coronary blood flow from prolonged hypotension following haemorrhage could result in heart failure Bing also (1951) stated that the coronary blood flow is about 80 millilitres of blood per 100 grammes of left ventricular muscle the A V oxygen difference is 12 volumes per cent, and the oxygen consumption of 100 grammes of left ventricular muscle is about 9 millilitres of oxygen Heart muscle therefore extracts almost a maximal amount of oxygen normally and myocardial asphyxia may result from reduced coronary blood flow

Opdyke and Foreman (1947) however, state that the work done by the heart (mean pressure times the cardiac output) is less under conditions of hypotension

Wiggers (1950) studied the effects of transfusion on bled dogs and found that the pressure developed in the ventricles at the beginning of systole (by the filling forces of a previous diastole) increased while at the same time the cardiac output fell According to Starling s (1918) concept this pressure change should lead to an increased cardiac output the reverse would indicate myocardial depression

Kohlstaedt and Page (1944) showed that during progressive circulatory failure both the systolic and diastolic heart volumes increased, the systolic size having greater volume change This suggested a lower stroke volume and an increased residual volume Wiggers (1947) postulated that cardiac stimulants might reverse circulatory failure after transfusion had failed, and Horton and Davison (1955) reported favourably on the use of strophanthin (Ouabain) during surgical operations

Effects on the periphery

Zweifach (1951) has made a special study of the changes in the peripheral vascular bed, which has been related in the main to the effects of haemorrhage He obtained a similar response in several different species of animals including rats guinea pigs cats and dogs Preliminary studies were made upon such tissues as the skin skeletal muscle, gut wall, intestinal mesentery and omentum A marked decrease in blood flow was found in the skin after blood loss amounting to only 2 per cent of body weight and the flow decreased with further deterioration Similar changes were also observed in muscle Most of his studies have been made on exteriorized omentum The blood from the omentum and mesentery drains into veins which empty into the portal system Zweifach (1951) did not claim that the circulation observed in the mesentery and omentum reflects the changes in all other organs Nor did he take the view that the changes he observed are necessarily the cause of the poor general condition after severe injuries this does not mean that they do not in fact play a major role The changes will now be described

Arrangements in the capillary network

Shorr Zweifach and Furchgott (1945) and Shorr Zweifach and Baez (1947) have shown that the architecture of the Furchgott capillary network in viscera is not the *simple arrangement of an arteriole dividing into many capillaries which finally unite* to form a venule They found two kinds of capillaries In one form termed metarterioles a channel with muscular walls passed directly through an arteriovenous capillary into a venule From the metarteriole sprang many capillaries—the true capillaries—which had frequent anastomoses before joining the main arteriovenous channel towards its venous end The direct channel remained open even though the tissue was in the resting state The musculature at the capillaries junction with the

metarterioles constituted the precapillary sphincter, the activity of which determines the volume and rate of capillary blood flow

Zweifach (1936) established the presence of vasomotion By this is meant periodic spontaneous, irregular contractions and relaxations, every 1–3 minutes of the metarterioles and precapillary sphincters Thus the blood flow through the capillary network is intermittent it is independent of the vasomotor state of the arterioles

Capillary tone

The true capillaries do not actively change their calibre It may be that by capillary tone is meant the state of elasticity of living endothelium (Fulton, 1955) These cells are held together by an intracellular cement substance Dilatation results in a stretching of the walls which may increase their permeability Chambers and Zweifach (1940) considered that the junctions between the endothelial cells are the most likely sites for the escape of large particles, such as plasma proteins, or for the leakage of smaller particles

Effects of injury on capillary circulation

Shorr and his colleagues (1947) described the effects of injury on the visceral circulation in animals They pointed to two phases of activity under experimental conditions The first phase, which they regarded as compensatory consists of an increase of vasomotion and an enhanced constrictive response of the metarterioles and precapillaries to the topical application of adrenaline In the second phase vasomotion ceases and there is less response to the application of adrenaline The blood in the capillaries stagnates and circulatory failure ensues from a lack of venous return At this stage of decompensation transfusion will produce only a temporary benefit The first phase occurs with the initial fall in blood pressure, and there is vasoconstriction in the arterioles At this stage transfusion can be effective in restoring the circulation

Vasodilator and vasopressor substances

During these phases certain substances appear in the blood stream Shorr, Zweifach and Furchgott (1945), and Chambers and Zweifach (1947) developed a technique for examining the blood of injured animals for vaso effective substances Samples of heparinized plasma, taken from an injured rat, were injected into the tail veins of a normal animal with its meso appendix exposed After a variety of injuries such as graded haemorrhage, the application of tourniquets, tumbling in a Collip–Noble drum, and muscle contusion the first manifestation was shown to be an increased vasomotion and an increase in the effect of a direct application of adrenaline to the mesenteric vessels This was the evidence for the presence of vaso excitor material (VEM) in the blood of the injured animal At a later phase when the changes became reversed vasodepressor material (VDM) was found The source of VEM appears to be the kidneys whereas VDM can be obtained from liver and muscle VDM in the blood meant that the animal would not respond to transfusion According to Mazur and Shorr (1948) it is likely that VDM may be the substance ferritin The evidence suggests that injury stimulates the kidney to produce VEM and this causes ischaemia in the liver, which then discharges VDM

The VDM neutralizes the VEM with the resulting relaxation of the capillary sphincters

There is some doubt about the action of VDM Fine and his colleagues (1952) prepared liverless and arenal dogs and injected large amounts of high potency ferritin intravenously into them without any depressor effect on the blood pressure notwithstanding that ferritin is oxidized by the normal liver and excreted by the kidneys

NERVOUS REACTIONS

A mechanical stimulus is difficult to grade in terms of its intensity, and the effects vary according to the anatomical site The stimulus may reflexly affect the heart causing it to beat faster or slower, or even, under certain conditions, to stop or the stimulus may if it is in the form of prolonged traction, obstruct parts of the circulation, so that either individual organs or a group of tissues are affected Whatever the precise traumatic mechanism, the result may be either hypertension or hypotension Of these two, the last is more often the most serious A brief interval of hypotension may have insignificant results but the seriousness of the situation depends on the extent and duration of hypotension

The reflex response to stimulation may affect respiration and this may secondarily affect the circulation The respiratory effects have been studied by Reeve Nanson and Rundle (1951) who found that the upper ligamentum teres was especially sensitive The use of endotracheal anaesthesia and muscle relaxant drugs has greatly facilitated operative procedures, and there are few, if any, reports to show that surgical manipulations under modern anaesthesia, properly administered, cause a serious deterioration of the general condition in patients not suffering from systemic disease, provided that the circulation is not obstructed and blood is not shed in more than minimal amounts (a few ounces) Under conditions of disease, for example peritonitis, or after blood loss, surgical manipulations may result in the vasovagal type of response which may be fatal Much depends on the previous state of the patient

CLINICAL CONSIDERATIONS

The work of Grant and Reeve (1951) established that, in the case of limb injuries which are the commonest form of injury the severity of the illness depends, in general on the amount of blood loss and that blood transfusion is the most effective form of treatment They estimated the blood volume by the Evans blue method and found that the larger the wound the greater the haemorrhage Grant (1954) showed that the two most important factors in assessing the state of a patient with a limb injury are the size of the wound and the level of the systolic blood pressure

Systolic blood pressure

The systolic blood pressure should be considered in relation to a number of factors including resuscitation pain emotional upset extremes of environmental temperature and infection Hypertension may result from pain and emotional upset, or the patient may develop hypotension with a slow pulse pallor of the

face and cold extremities A cold environment produces vasoconstriction and with this the blood pressure may be raised a warm environment provokes the opposite though the face may remain pale Infection is likely to have developed after 8 hours following the injury Transfusion may produce a reaction which complicates the clinical signs, for example the amount of transfusion may be grossly inadequate and yet it will result in an increase in blood pressure possibly from the pharmacological effects of blood Unless one of these factors pre dominates a systolic pressure of at least 100 mm Hg means that the blood volume is probably not less than 70 per cent of normal if it is below 100 mm Hg the blood volume is likely to be less than 70 per cent of normal

Size of the wound

The size of the wound can be judged by comparison with the observer s hand which amounts to about half a litre The open hand can be used for assessing the more superficial types of wound It is of some assistance to know that the foot, knee forearm and upper arm have roughly the same volume amounting to two or three hands, while the leg volume is four or five hands and the thigh is from ten to twelve hands Wounds having a volume of less than one hand are classed as small two to three hands are moderate, three to five hands are large, and five hands or more are very large injuries

Clarke and Fisher (1956) have devised valuable aids for training observers to recognize the extent of tissue damage tissue swelling and blood loss They have constructed a series of cubes of known volumes from half a litre upwards which help in assessing the extent of tissue damage In addition they have cut out known volumes of surgical felt which can be wrapped round a limb or even the trunk these aid the observer in estimating the extent of swelling They have also explained the necessity for spreading out surgical swabs instead of viewing them in one compact bundle for the assessment of blood loss at operation Barbour (1957) has shown that as much as 1 500 millilitres of blood may be extravasated within the hip or thigh without any outward sign of its presence This means that if the extent of outward swelling of a part is used by itself as a guide to blood loss this is likely to be a gross underestimate

Grant and Reeve (1951) found that patients with small wounds generally lost about 10 per cent of their normal blood volume (predicted from their height) 20 to 40 per cent was lost in the case of moderate wounds 40 per cent in large and 50 per cent or more in the very large limb injuries Thus the required amount of transfusion can be predicted from the extent of tissue damage

Transfusion

Grant (1954) judged that transfusion is necessary in all patients when the extent of the wounds and the circulatory state are such as to suggest that the blood volume is below or not much over the 70 per cent level Whole blood is the best fluid to transfuse and there must be the minimum of delay in starting If plasma or other substitutes have to be used first anaemia should be treated later The rate of trans fusion should be between 5 and 15 minutes per pint until sufficient has been given Restoration of the blood pressure to 100 mm Hg merely means that the blood volume has reached the 70 per cent level and if transfusion is stopped at this

time it is likely that the patient's condition will deteriorate if he is subjected to further stresses, for the circulation is unstable. That the blood volume has been returned to near normal is shown when the blood pressure returns to normal, and the pulse rate slows with a change from vasoconstriction to vasodilatation. Grant (1954) recommended that the blood volume should be restored to about 90 per cent of the normal. He considered that a pint bottle of blood could be expected to raise the blood volume by 5-9 per cent for the average man.

In the case of a patient who has received a limb injury and subsequently develops hypotension, tachycardia and vasoconstriction, the need for blood is urgent because the blood volume is likely to be so reduced as to endanger life; the situation in a patient with an abdominal injury may be different, although he may show the same triad of signs; in the case of peritonitis, as Grant and Reeve (1951) found, the blood volume may be normal. On the other hand, the blood volume may be reduced on account of haemorrhage and blood is required urgently. The appropriate treatment can best be decided when the abdomen is opened. Patients with peritonitis do not respond to blood transfusion in the same way as those with limb injuries. The work of Grant and Reeve applies in the main to young fit subjects. The older the patient the more difficult will it be to assess his general condition; furthermore, injuries other than those affecting the limbs and abdomen are complicated by additional factors, for example, pneumothorax, in the case of chest injuries.

Howard (1953) studied the circulatory reactions of men wounded in the Korean war. He judged the adequacy of blood transfusion by the restoration of blood pressure in a group of patients having limb or abdominal injuries but it appears that he did not differentiate between the two types of injury in this respect notwithstanding the work of Grant and Reeve. The evacuation time was $3\frac{1}{2}$ hours and no difficulty was experienced in restoring the blood pressure by transfusion before operation. The blood pressure fell at operation and often remained low after operation; when it fell to zero the patients could not be resuscitated. Individual patients received quantities of between 15 and 42 pints of blood, mainly after operation. Despite these transfusions the venous pressure was not found to be raised, the veins being in a state of constriction, and increased blood volumes, as measured by the Evans blue or radioactive chromium methods, were seldom found. It was felt that the amount of transfusion greatly exceeded the external loss of blood; nevertheless, the impression was gained that many owed their lives to transfusion.

Firt and Hejhal (1957), after an extensive investigation in dogs, have concluded that rapid transfusion by the intravenous route of blood can produce pulmonary vasoconstriction and depression of myocardial function. The cardiac effects during transfusion are not due to the blood *per se* but can be related to the amount of citrate. The dose of citrate which affects the heart is decreased under certain conditions such as anaemia, liver damage, cardiac disease and shock. Blood without citrate can be safely given at rates many times greater than citrated blood. They consider that an advantage of intra-arterial transfusion is that the citrate concentration reaching the heart is less than when it is administered intravenously. The effect of citrate during transfusion can be counteracted by giving calcium and procaine intravenously. This work indicates that one cause of failure of the response to transfusion may be citrate poisoning.

Abdominal injuries and liver function

A finding of considerable interest was the greater impairment of liver function and reduction of renal blood flow and glomerular filtration (measured by the para amino hippuric acid and inulin clearance) in the abdominal than in the limb injuries group (Howard 1953) However, since there was a greater mortality in the abdominal group this may not reflect a difference between the types of injury, it may be related to blood loss Except in the case of renal failure the deaths occurred mainly within 36 hours of injury Extensive autopsy studies failed to reveal consistent evidence of a site with blood accumulation the liver and spleen were not enlarged and blood was not found in excess in the gastro intestinal system Both Howard (1953) and Grant and Reeve (1951) found a state of haemodilution with limb injuries and haemoconcentration with abdominal injuries

Infective factor

Beecher (1949) has used blood volume loss as a means of grading the effects of injury, but this does not allow for the effects of infection Evidence has been produced in animals of an infective factor which accounts for the state of irreversibility to transfusion after haemorrhage (Fine 1953) A large portion of liver was removed from a dog in poor circulatory condition and after this had been mashed up it was transferred into the peritoneal cavity of a guinea pig The guinea pig then died without signs of peritonitis, although death could have been prevented by the administration of *Clostridium* antitoxin If a liver mash is taken from a dog suffering from haemorrhage and injected into a second dog also suffering from haemorrhage, the latter dies but its death can be prevented by penicillin therapy

Frank and his colleagues (1952) administered aureomycin to dogs and subjected them to a haemorrhagic period which would prove lethal to 88 per cent of dogs without aureomycin Of the dogs receiving this drug 88 per cent recovered Hence bacterial action aids in the development of irreversibility after blood loss

Agglutinated red cells

Knisely and his colleagues (1950) describe a condition characterized by blood vessels obstructed with soft masses of agglutinated red cells The loss of cells from the circulating blood would result in a haemodilution as measured by the haematocrit of blood taken from unobstructed vessels It may be that changes of this kind occur in the liver and other vital organs they can be detected in the conjunctival vessels of the eye after crushing injuries but they are not seen after pure haemorrhage These findings may have a bearing on the interpretation of blood volume estimations in injured patients which depend on the haematocrit

PART 2 ANAESTHESIA AND THE CIRCULATION

EFFECTS OF ANAESTHETICS ON THE CARDIAC OUTPUT

Judgment of the precise effects of anaesthetics upon the heart is difficult owing to the complexity of homeostatic mechanisms The effects on the isolated organ give some indication these have been studied by a number of workers

Behaviour of the isolated dog's heart

Prime and Gray (1952) produced evidence of cardiac depression in the dog heart-lung preparation due to ether, cyclopropane and thiopentone. The rise in venous pressure and fall in cardiac output which they found could result from a concentration of ether which is ' barely sufficient to produce unconsciousness in the human subject. Concentrations of about 100 milligrams per 100 millilitres of blood produced irreversible damage. The explanation may be that the dog's heart is more sensitive than the human heart to these drugs. But whatever be the sensitivity of the dog's heart to anaesthetic agents it is not unduly sensitive to muscle relaxant drugs. Prime and Gray (1952) showed that the relaxants gallamine triethiodide, decamethonium iodide and Win 2747 had no effect on the isolated heart. Gray and Gregory (1948) also demonstrated in the dog heart-lung preparation that *d*-tubocurarine chloride, in doses of about 70 milligrams had no effect on the cardiac output, arterial blood pressure or coronary blood flow, even when the heart had been affected previously by thiopentone, adrenaline or hypoxia.

Effects on the intact human heart

Morphine and atropine

Prime and Gray (1952), utilizing the Fick principle, measured the cardiac output before and during surgical operations in a group of 31 patients who were considered to be free of cardiovascular abnormalities. They found a slightly increased cardiac output and forearm blood flow after premedication with morphine and atropine. This was attributed to the emotional state of the patients rather than to the effects of the drug.

Ether and cyclopropane

With ether and cyclopropane anaesthesia Prime and Gray (1952) found a transient initial increase in cardiac output and forearm blood flow. These changes were followed by a progressive fall in cardiac output, and the forearm blood flow declined to levels below the values obtained before anaesthesia. In the case of the combination of thiopentone, nitrous oxide and oxygen (50 per cent) with *d*-tubocurarine chloride, although the blood flow in the forearm increased markedly in the initial stage, there was no change in cardiac output. The raised cardiac output with ether and cyclopropane in human subjects was an unexpected finding in view of the effects in the heart-lung preparation. It is possible that the cause was due to a nervous reflex.

Morphine scopolamine

Johnson (1951) made a comparison in measuring the cardiac output by the Fick principle and by the dye method (Hamilton and his colleagues, 1932) in man. In 130 almost simultaneous comparisons, the means showed a close approximation. In addition the dye method was used to estimate the pulmonary blood volume, which is the volume of blood in the lungs up to and including the capillaries and the left side of the heart. The pressures in the different cavities of the heart were also measured.

Morphine scopolamine in normal dosage had little circulatory effect, though overdosage could cause a reduction in cardiac output. The cardiac output during

a short period of light ether anaesthesia rose and continued to increase with deep anaesthesia. When the anaesthesia was prolonged the cardiac output diminished. The pressure and resistance in the systemic circulation usually decreased. However, the pressure in the pulmonary circulation rose considerably, due to vaso-constriction on its arterial side, and the power of the right ventricle increased in consequence. In prolonged and deep ether anaesthesia, he found that there was a tendency for the pulmonary blood volume to decrease, otherwise it was unaffected.

Barbiturates

With barbiturate anaesthesia (Narkotal) the cardiac output, stroke volume and pressure in the systemic circulation, and the pulmonary blood volume all decreased, the pulmonary volume markedly. Johnson (1951) argued that since the resistance* in the systemic circulation was constant, the blood probably accumulated on the venous side of the circulation. As would be expected, the use of a relaxant with barbiturate anaesthesia made the circulatory changes less pronounced.

Spinal anaesthesia

A decreased cardiac output, stroke volume and systemic pressure were found during spinal anaesthesia, as well as a displacement of blood from the lungs to the veins in the systemic circulation. Contrary to what might be expected, the fall in blood pressure was mainly caused by the decreased cardiac output and was rarely due to diminished resistance. The fall in blood pressure could be counteracted by lowering the head of the operating table; this procedure also increased the cardiac output, stroke volume and pulmonary blood volume. Oxygen administration had no effect on the cardiac output, the blood pressure or the distribution of blood.

Johnson (1951) found that the blood in the lungs amounted to almost one litre, which is more than is needed for the purposes of respiration, and he suggested that the pulmonary blood bed functions as a reservoir. Changes in the pulmonary blood volume did not affect respiration, and although the pressure in the pulmonary artery bore no relation to the pulmonary blood volume, this volume was related to the stroke volume of the heart, the filling of the left ventricle being directly proportional to the amount of blood in the lungs.

Pugh and Wyndham (1950) have confirmed that the fall in blood pressure during spinal anaesthesia (to the level between the fourth and sixth thoracic segments of the cord) is accounted for in the main by a fall in cardiac output. Reduction in peripheral resistance was present but was not marked. Acute hypotension with fainting occurred when the head was raised, and vasodilatation became evident above the analgesic level. The reduced cardiac output with high spinal anaesthesia has also been confirmed by Lynn and his colleagues (1952).

Cyclopropane

De Wardener and his colleagues (1953) found that the cardiac output was decreased under the conditions of haemorrhage during light anaesthesia with cyclopropane following thiopentone induction. That this was not solely due to

*Resistance $= \dfrac{1332 \times Pm}{\text{Cardiac output}/60}$ Pm = mean arterial pressure in mm Hg

the loss of blood is shown by De Lee and his colleagues (1953) who found a reduced cardiac output (Hamilton dye method) in relation to light anaesthesia with this combination without haemorrhage

Li and Etsten (1957) made observations on 14 patients *before surgery* using cyclopropane in a closed circuit after a preliminary nitrogen washout, but without a barbiturate induction They measured the concentration of cyclopropane in the blood and at the same time used the encephalograph as a guide to the depth of anaesthesia Premedication was confined to morphine and scopolamine They found that the left ventricular work was not significantly changed, although the cardiac output and heart rate were reduced during both light and deep anaesthesia They attributed the reduction in cardiac output to the slowing of the heart rate and to an elevation of peripheral resistance, which was also found, together with a raised pressure in the pulmonary artery and in the central venous system, these last observations were taken to mean that cyclopropane has a pressor effect on the systemic and pulmonary circulation

According to Sarnoff (1955) a decrease in ventricular stroke work associated with a raised end diastolic ventricular pressure suggests an impairment of cardiac function Li and Etsten (1957) stated that when cardiac function is impaired the response to ventricular filling is affected but changes in the cardiac output and central venous pressure do not readily reflect cardiac function Etsten and his colleagues (1953) found in man that the end diastolic ventricular pressure was not raised during cyclopropane anaesthesia and Li and Etsten (in Press) have confirmed this in dogs finding that the right and left end diastolic ventricular pressures were not elevated during cyclopropane anaesthesia despite a reduction in cardiac output They were therefore of the opinion that the function of the heart is not impaired during cyclopropane anaesthesia

Disturbances of the cardiac rhythm

Cardiac arrhythmias are common but often pass unrecognized their effects on the patient s general condition being difficult to detect in many instances This incidence will depend upon the number of times that certain anaesthetic agents are used (Morris Noltensmeyer and White, 1953) The irregularities related to ether anaesthesia usually affect the pacemaker and do not appear to have any serious import whereas the irregularities of chloroform cyclopropane and trichloroethylene affect the action of the ventricles and these arrhythmias are potentially the precursors of rhythms which endanger life they are characterized by multifocal ventricular extrasystoles which may change to ventricular fibrillation, particularly under the influence of adrenaline The experiments described by Raventos (1956) suggest that the sensitivity of the heart to adrenaline is increased to a lesser extent by halothane (Fluothane) than by cyclopropane but to a greater degree than by chloroform

Although the arrhythmias occurring during ether or thiopentone anaesthesia are generally considered to be minor events, they may be associated with cardiovascular changes because certain arrhythmias affect function in the conscious state Auricular flutter causes a reduction in cardiac output, with increases in the arteriovenous oxygen difference in the circulation time and in the venous pressure (Lequime 1940 Stewart and his colleagues 1938) Auricular tachycardia can cause circulatory collapse (Altschule 1954) Although there are conflicting results

reported on the effects of the arrhythmias on cardiac function there are many references to a reduction in cardiac output (Altschule, 1954) This change is likely to add to the stress of a surgical operation to the general circulatory detriment

Meek (1940) has shown experimentally how arrhythmias develop under cyclopropane anaesthesia if pulmonary ventilation is deficient, and Johnstone (1950) has confirmed this in man Brown and Millar (1952) have shown how changes in carbon dioxide tension when pushed to what must be regarded as extreme limits, can result in ventricular fibrillation in dogs A mixture containing from 30 to 40 per cent carbon dioxide was inhaled for 4 hours in the anaesthetized state The rapid reduction of alveolar carbon dioxide tension at the end of this period resulted in ventricular fibrillation and death in 11 of the 15 dogs In two animals the reduction in carbon dioxide tension was made more gradually and they survived without arrhythmias Although these changes in concentrations are extreme it is conceivable that the arrhythmia may develop with a lower level of change in conditions of circulatory instability Scherf Goldfarb and Bussan (1955) have drawn attention to the effect of hyperventilation (voluntary overbreathing) in man in diminishing or abolishing various cardiac arrhythmias They are unable to explain the mechanism for these changes but believe that they are in some way related to the increased *p*H of arterial blood or to changes in electrolyte pattern

Cardiac arrest

Wylie (1956) stresses that cardiac arrest should be anticipated and precautions taken for the immediate application of treatment by cardiac massage, so that the circulation of blood may be restored within 3½ minutes The details of the treatment of cardiac arrest and ventricular fibrillation have been well described by Milstein (1956)

Pneumo massage

Intracardiac drugs are ineffective and may be dangerous (McMillan Cockett and Styles, 1952) and cardiac massage itself may result in cardiac damage To prevent this Bencini and Parola (1956) have applied intermittent positive pressure with air or oxygen through a flanged cannula inserted into the pericardial sac—pneumo massage In dogs this method produced a systolic pressure of 100 mm Hg but pressure measurements in the right auricle and jugular vein indicated little venous return It would be interesting to know whether the venous return could be aided by the application of a negative pressure phase The method can be applied only when the pericardium is intact

Ventricular standstill

The differentiation between cardiac standstill and ventricular fibrillation may be difficult clinically but the difference can readily be seen on a cathode ray tube which is connected to a continuous electrocardiograph The application of defibrillating electrodes to the heart itself requires a wide exposure within the thorax For the treatment of ventricular standstill Zoll (1952) has devised an apparatus which allows for the passage of a succession of impulses which are too small and too short to produce ventricular fibrillation but are sufficient to stimulate the ventricles through the intact chest wall Leatham Cook and Davies (1956) have

made an electric stimulator for the same purpose, and have incorporated a warning device which comes into action if no QRS pattern is received from the continuous electrocardiogram

Controlled cardiac arrest

Melrose and his colleagues (1955) have described a technique for arresting the heart's action in animals by the injection of potassium citrate into the coronary vessels, and have performed token operations before restarting the heart by a transfusion with blood pumped into the circulation using the heart-lung machine (Melrose, 1955) after removing the aortic clamp This method was effective in the dog's heart at normal and hypothermic temperatures down to 26° C They found that the oxygen consumption of the quiescent heart was low, and at normal body temperature an arrest of coronary circulation for 15 minutes did not prevent a return to normal under these conditions

Barbiturates

Edwards and his colleagues (1956) have noted that a number of deaths reported to the Association of Anaesthetists of Great Britain and Ireland have resulted from administering barbiturates intravenously, particularly thiopentone, during the induction period, when attention has not been paid to the circulatory condition of the patient

Atropine

Atropine and neostigmine, given simultaneously by vein at the end of operation in order to reverse the action of relaxants, may cause sudden circulatory failure (Macintosh, 1949 Clutton Brock, 1949, and Hill, 1949) Bain and Broadbent (1949) have stated that the first effect of atropine given intravenously may be to slow the heart rate if this coincides with a similar effect of neostigmine, then the heart may stop beating Even when both drugs are given at different times the heart may become abnormally slow To prevent further slowing Hunter (1953) recommends a second dose of atropine He was unable to demonstrate the effect of atropine in slowing the heart

Effects of anaesthetics on the baroreceptors

Robertson, Swan and Whitteridge (1956) recording from single units of the aortic and carotid sinus nerves in cats, demonstrated an increase in sensitivity from the baroreceptors during exposure to volatile anaesthetics such as ether, chloroform and trichloroethylene

EFFECTS OF ANAESTHETICS ON THE BLOOD FLOW THROUGH VARIOUS ORGANS

Blood flow through skin and muscle

The flushing of the skin in the exposed parts under the initial influence of ether and cyclopropane anaesthesia contrasts with the pallor of chloroform, and the pallor which characterizes the recovery period of them all Part of the pallor

with chloroform is probably due to the fall in blood pressure A peculiar waxy pallor of the face is the rule with chlorpromazine

Abramson Grollman and Schwartz (1941) measured the blood flow through the hand and forearm in 12 subjects representing flows through skin and muscle respectively, using the venous occlusion plethysmographic method with cyclopropane anaesthesia They found an increase in flow in both vascular beds which was approximately four times that of the control values There were no definite changes in blood pressure or pulse rate coincidental with these changes

It is of interest to consider the time relation of these changes in blood flow Lynn and Shackman (1951) studied the circulation through the calf hand and foot, during surgical operations performed with general anaesthesia The anaesthetics were cyclopropane ether trichloroethylene, nitrous oxide and oxygen, thiopentone and gallamine triethiodide in various combinations Two main groups of patients were studied In the first group the operations were brief and relatively minor, as for example those for the repair of a hernia, in the second group, longer operations such as partial gastrectomy were performed Increased limb blood flows were found during the whole period in the first group and also during the earlier phases of the second group During the more prolonged procedures the limb flows became reduced in most instances to values equal or below the pre anaesthetic level During the initial increase in blood flow through the skin and muscle which takes about 30 minutes to develop during anaesthesia Shackman and Graber (1952) found a close time relationship between these changes and a reciprocal change in rectal temperature (measured with a copper constantan thermocouple)

Foster and his colleagues (1954) have made a study of the effects of chlor promazine on the peripheral circulation in man, including its effects on blood flow through the hand forearm and calf as well as changes in pulse rate and blood pressure The effects on the blood pressure and pulse rate were variable, the most consistent being a rise in pulse rate and a fall in blood pressure, the values being slightly greater in conscious than in unconscious subjects In conscious subjects chlorpromazine produced a 284 per cent increase in blood flow through the hand, and a 72 per cent increase in flow through the forearms and calves After an infusion into the brachial artery in conscious subjects, chlorpromazine caused a 50 per cent increase in the blood flow through the hand, this indicates a peripheral action Since the effects from intravenous injections were significantly greater than the arterial effects, it is suggested that the drug has both central and local actions When the brachial plexus was blocked chlorpromazine caused an increase in blood flow through the hand over and above that produced by the block this indicates a direct action on the blood vessels

The application of cold to the forehead or chest normally causes vasoconstriction in the hand after intra arterial injections of chlorpromazine the cold constrictor test reduced hand blood flow by 25–80 per cent whereas after intravenous injections the decrease was only 5–10 per cent This suggests an interference with vaso constrictor influences it is possible, however that the afferent side of the reflex arc was involved since the unpleasant effects of the ice on the skin were lessened after chlorpromazine No significant changes in hand blood flow reduction by noradrenaline were produced after chlorpromazine administration Chlor promazine given intra arterially reduced vasoconstriction due to adrenaline in the hand, but when chlorpromazine was given intravenously it reversed the action

of adrenaline This suggests that it would be useless and even dangerous to treat hypotension due to chlorpromazine by adrenaline, noradrenaline should be used for this purpose, probably in larger doses than usual

Shackman and his colleagues (1954) found that the 'lytic cocktail', a mixture of pethidine, promethazine and chlorpromazine, produced an increased peripheral blood flow, an increased pulse rate and a fall in blood pressure, a rise in cardiac output and a decrease in the over all systemic resistance In the unexposed patient it did not produce hypothermia, nor did it affect the oxygen uptake

Blood flow through the kidney

Miles and De Wardener (1952) showed that, when the nerve supply to the kidney was cut off ether or cyclopropane given by inhalation did not produce vasoconstriction, whereas in the intact animal a sustained vasoconstriction resulted Bayliss and Brown (1940) found that ether did not affect the creatinine clearance in decerebrate dogs with denervated kidneys It would appear that the vaso constriction due to ether and cyclopropane has a neurogenic mechanism The vasodilatation found in the organ which is not connected to the nervous system may be due to a local action of the anaesthetic agent affecting the blood vessels directly

Blood flow through the cerebrum

Wechter, Dripps and Kety (1951), using the nitrous oxide method for estimating cerebral blood flow found that there was an adequate flow during thiopentone anaesthesia in man despite the fact that the utilization of oxygen in the cerebrum was significantly depressed

Blood flow through the liver and splanchnic regions

Shackman, Graber and Melrose (1953), working on the blood flow through the liver during general anaesthesia—using thiopentone, *d* tubocurarine chloride cyclopropane and oxygen—found a 30 per cent decrease in the estimated hepatic blood flow (EHBF) in relation to the pre anaesthetic values They used the bromsulphthalein extraction test before surgery By multiplying the EHBF by the arterio hepatic venous oxygen difference they deduced the liver and splanchnic oxygen consumption This value decreased by 34 per cent which is greater than the figure of 22 per cent found by Shackman, Graber and Redwood (1951)

These changes occurred independently of the level of systemic blood pressure It would appear that there is a liver and splanchnic vasoconstriction when vaso dilatation is present in the skin and muscles No clinical signs of liver dysfunction were found but it may well be that vasoconstriction in this region is harmful when the liver is already in a state of disorder The reduced oxygen consumption suggests that the reduction in blood flow may have a hypoxic effect on the tissues although this does not necessarily follow since their requirements may still be covered It would seem a wise decision to avoid prolonged operations whenever possible in patients with liver dysfunction and also to ensure adequate replacement of blood loss

It is of interest at this stage to note that Lynn and his colleagues (1952) have found, under the conditions of high spinal anaesthesia that the liver and splanchnic oxygen consumption do not fall notwithstanding a reduction in the EHBF occurring coincidentally with a marked hypotension and reduced cardiac output

ANAESTHETIC TECHNIQUE AND ITS EFFECTS ON THE CIRCULATION

Depth of anaesthesia

The introduction of curare by Griffith and Johnson (1942) resulted in a radical change in anaesthetic procedure. The maintenance of deep anaesthesia became no longer necessary, and those who held that deep anaesthesia protected the patient from the effects of surgery have had their premise put to the test, for light anaesthesia has now become a routine even for major surgery.

Brown and Sellick (1955), however, stated that the signs of 'too light a level of analgesia are in many cases identical with those of commencing shock'. They give seven indications for giving more analgesic drug: (1) movements of the facial and hand muscles; (2) increase in pulse rate and fall in blood pressure which cannot be explained by the surgical manipulations occurring at the same time; (3) dilatation of the pupil; (4) secretion of tears; (5) vasoconstriction, a fall in skin temperature and a delayed capillary refilling time; (6) sweating, and (7) the onset of a slight increase of the resistance to inspiration and prolongation of expiration—provided the presence of sputum in the air passages can be excluded. The evidence to support the reliability of these indications is, however, lacking in the paper in question, and Gray (1957) stated that 'the experience of the last ten years has shown that light anaesthesia does not conduce to circulatory collapse despite the fact that patients are often moving, frowning or showing other reactions to stimuli'. It is of interest, therefore, to see what happens to the circulation in man during prolonged light anaesthesia.

De Lee and his colleagues (1953) have shown that after an induction with 0.4 to 0.5 gramme thiopentone, light cyclopropane anaesthesia produced a decreased cardiac output with muscle vasodilatation and renal vasoconstriction, the total peripheral resistance being slightly reduced. Muscle vasodilatation decreased later though the renal vasoconstriction persisted and the cardiac output fell. There was a rise in the total peripheral resistance and the blood pressure was maintained. These authors stated that 'a very light anaesthetic level was maintained in order to facilitate keeping the level as constant as possible. In every case reflex muscular activity was observed from time to time'. These observations were made on six healthy male volunteer patients before and during operations for varicose veins. The cardiac output was measured by the Hamilton dye test and the renal circulation was studied by the inulin and para amino hippurate (PAH) clearances.

The circulatory effects of haemorrhage during prolonged light anaesthesia in man have been investigated by De Wardener and his colleagues (1953). The same anaesthetic procedure was used as when prolonged light anaesthesia was studied. They found that the effects of blood loss up to 1,460 millilitres were not identical with those occurring in the conscious state. According to Barcroft and his colleagues (1949), haemorrhage of this degree in subjects in the supine position caused vasovagal fainting and vasodilatation in the muscles. De Wardener and his colleagues (1953) found that under anaesthesia there was evidence of muscle vasoconstriction after haemorrhage. In two of the subjects the blood pressure reached a level below 40 mm Hg, and bradycardia developed, but there was no evidence of muscle vasodilatation. This suggests that the cause of the hypotension

in the subjects under anaesthesia was different in the conscious state It was found that the cardiac output was still reduced in these subjects after partial retransfusion, which may account for the hypotension Their evidence suggests that controlled haemorrhage during surgical operations acts by abolishing the vasodilatation due to anaesthesia Hence, in this case it is not necessary to maintain a reduction of blood pressure to limit bleeding Further observations showed that there were no significant changes in renal blood flow, but cardiac output and intrathoracic blood volume were decreased by the haemorrhage

Kitchin and his colleagues (1953) confirmed the vasodilatation in muscle during light anaesthesia with cyclopropane but they have shown in addition that there is a decrease in the blood flow through muscle with deep anaesthesia They compared simultaneous measurements of blood flow in two forearms In one forearm, the radial, median and ulnar nerves were blocked with a local anaesthetic Anaesthesia was induced with either cyclopropane or with 0 5 gramme of thio pentone They found a rise in muscle blood flow in the normal forearm, and no increase in the muscle flow of the nerve blocked limb This shows that an intact nervous supply is necessary for the production of vasodilatation by cyclopropane Cyclopropane was acting either centrally on the vasomotor centre or peripherally on the vasomotor neuromuscular mechanism Deep anaesthesia reduced the flow in both blocked and unblocked forearms When the absorber was cut off to allow carbon dioxide to accumulate there was no change in the blood flow The authors suggested that the vasoconstriction of deep anaesthesia may be due to an action of the drug on the metabolism of the cells of the walls of the blood vessel or to the release of vasoconstrictor material

On the recording of blood pressure

Failure to provide for blood pressure estimation during major surgical operations may put the anaesthetist at a disadvantage he cannot be sure that a hypotension is not due to the anaesthetic procedure if no value has been obtained before the skin incision If the pressure is maintained for about 15 or more minutes and falls after the incision is made, then it is likely to be due to surgical manipulations even though blood loss has been minimal A fall in pressure occurring without much surgical manipulation after haemorrhage is an urgent reminder that the circulation is unstable and that transfusion is a necessity

Too much recording of the blood pressure is likely to distract the anaesthetist from his administration particularly when the operation is a short one, too little recording may result in the anaesthetist wondering when a state of hypo tension has begun this is a point of some value in deciding the nature of a given circulatory collapse Certain periods during operations are likely to result in hypotension (Harbord 1950) and at such times more frequent estimations are necessary If the diastolic pressure is taken as well as the systolic pressure the labour and time of the estimation will be doubled and it is doubtful whether the information is worth while It is even doubtful whether the method for determining the diastolic point is reliable by ordinary sphygmomanometry, as in normal subjects the sounds may be heard on occasions practically down to zero although Johnson (1951) stated that in a subject with healthy circulation, a rise in pulse rate to over 100 beats per minute and a fall in pulse pressure to less than

30 mm Hg implies a diminished pulmonary blood volume and therefore a latent or manifest peripheral circulatory insufficiency

The absolute level of the systolic blood pressure plus or minus 5 mm Hg is important and when considering hypotensive states the duration of a given level is a factor which may decide the fate of the patient

The development of blood pressure followers (Green 1955) which function by means of a cuff on a finger if they can be made to withstand the conditions prevailing in the operating theatre may relieve the anaesthetist considerably

Changes in blood pressure when the anaesthetic inhalation ceases

At the end of operation various changes may be apparent to the anaesthetist who may judge that the patient's general condition has deteriorated Harbord (1947) drew attention to an abrupt fall in blood pressure when inhalation apparatus was withdrawn and suggested that the phenomenon was due to a change in the carbon dioxide stimulus

Dripps (1947) has presented evidence to show that the decreases in blood pressure when the mask is removed at the end of cyclopropane anaesthesia are related partly to a previously raised pressure of carbon dioxide in the arterial blood during anaesthesia The phenomenon was at first called "cyclopropane shock" but the change is not confined to this agent

Price (1951) showed that an increase in the central venous blood pressure occurred uniformly with cyclopropane anaesthesia He concluded that a respiratory acidosis could also affect the venous side of the circulation He found also that the extent of the increase in the central venous pressure (CVP) was a function of the concentration of cyclopropane in the blood (Price 1953) It occurred whether or not there was an increase in carbon dioxide tension The venous system is also affected because the venous pressure was found to be raised with respiratory acidosis The CVP was inversely related to the heart rate but this was not the cause itself because atropine increased the heart rate and reduced the CVP When the concentration of cyclopropane was suddenly reduced the arterial pressure rose sharply and the CVP fell promptly This change suggests that the heart ejects additional blood and depletes the central veins An increase in the peripheral resistance could contribute to the raised arterial pressure but this would not account for the fact that the pressure does not remain elevated It may be that the raised CVP signifies a decreased cardiac competence

Hypotensive technique

(See Chapter 14)

Hypothermia

(See Chapter 9)

Artificial respiration

The use of artificial respiration by anaesthetists has increased with the advent of muscle relaxant drugs The term "controlled respiration" is misleading for the anaesthetist merely controls the pressures in the airway Controlled inflations or inflations and deflations, where this is applicable would be preferable terms

There is a tendency in some quarters to increase the use of artificial respiration,

particularly with the development of pulmoflators This seems rational in the case of certain operations lasting for half an hour or more Spontaneous breathing under anaesthesia is usually associated with some degree of defective carbon dioxide elimination (Harbord 1955) If the subject is otherwise fit, this may not affect the issue unless the carbon dioxide accumulation is considerable when it may have pressor effects on the blood pressure The opposite tendency namely hyperventilation, though it may have dangers, appears to be deliberately used in some centres (Crafoord 1938) Hypotension may then be produced It would seem that a slight degree of over ventilation or under ventilation is not harmful and the circulatory changes are not marked The effect of artificial ventilation on the circulation has been discussed elsewhere in this volume (*see* Chapter 7)

Full muscular relaxation

Thomas (1957) argues that the fall in blood pressure observed after the intravenous injection of *d* tubocurarine chloride is due to this drug because it occurred within 1–2 minutes of the injection he also found a relationship between the dose and the extent of the fall in pressure The same fall in blood pressure was not found when suxamethonium was substituted This work needs confirmation the difficulty is to eliminate other depressor factors

CLINICAL CONSIDERATIONS

The anaesthetist has it within his power to wreak considerable circulatory havoc or to conduct the anaesthesia in such a way as to produce relatively slight disturbance The agents themselves are toxic to the heart muscle and if given intravenously too rapidly they can arrest the action of the heart Although reduction of the cardiac output by an arrhythmia is not necessarily dangerous to the life of the patient it may affect the general condition adversely in certain circumstances particularly in the case of the instability of the circulation due to haemorrhage, or when adrenaline is combined with certain agents

Although vasoconstriction in the liver and splanchnic areas may not be harmful when due to an anaesthetic agent in a normal subject, this condition may be *increased by haemorrhage and the vasoconstriction in patients with deficient liver* function may be disastrous In such instances light anaesthesia is likely to be much less harmful than deep anaesthesia

Until evidence that light anaesthesia is harmful *per se*, there seems to be every reason for using techniques which combine light anaesthesia preferably with nitrous oxide and oxygen, and muscle relaxant drugs with or without analgesic drugs

The suggestion by Beecher and Todd (1954) that the increased use of relaxant drugs carries a greater mortality may not mean that the drugs are to blame the fault probably lies with the anaesthetist (Editorial 1957) it may be due to a failure to treat respiratory depression

Although there may be good reasons for using artificial respiration from the pulmonary ventilation viewpoint the technique of intermittent positive pressure alone may embarrass the circulation under haemorrhagic conditions The addition of a sub atmospheric pressure phase during expiration is recommended both from the point of view of respiration and the circulation in patients with a closed chest

Grant and Reeve (1951) showed that if a patient with a limb injury is treated

adequately by transfusion with whole blood, given in time, he should generally go through operation and recover, no matter which of the standard forms of anaesthesia is employed provided faults in technique are avoided and provided blood loss is made up at operation A patient who is *in extremis* from loss of blood may die during the induction of anaesthesia with small doses of any agent It may be that this is the explanation of at least some of the deaths reported by Halford (1943) who condemned the use of intravenous anaesthesia in these patients Beecher (1946) recommended thiopentone in 2 5 per cent strength for operations which are likely to last 45 minutes or less in the ' lightly wounded He decried its use in the patient whose general condition is poor, yet despite this he regarded thiopentone as one of the three most important anaesthetic agents for use in military medicine (Beecher, 1949) There is no doubt that many injured patients benefited from its use in World War II

Grant and Reeve (1951) showed that the signs found in an injured patient had a differing significance according to the circumstances and to the type of injury They found that tachycardia hypotension and vasoconstriction in a patient with a limb injury, recently acquired, signified that the patient had a low blood volume, whereas a patient with an abdominal injury might have a normal blood volume The patient with the limb injury would respond well to blood, the one with the abdominal injury would not necessarily do so

It is clear from work on animals that after a certain period, hypotension from blood loss leads to changes characterized by a failure of the organism to survive even though the blood is replaced Hershey, Zweifach and Rovenstine (1953) have studied this phenomenon in relation to the effects of ether cyclopropane and thiopentone following haemorrhage in dogs They demonstrated how each of the agents had a deleterious effect on the peripheral re adjustment mechanisms within the capillary bed and further that this became greater with an increasing depth of anaesthesia

It is interesting to note that in the case of autonomic blockade from dibenamine there is a decrease in muscle tone in vessels which are under sympathetic nervous control (Nickerson 1949 Grimson 1949) The activity of the terminal arterioles metarterioles and precapillaries which are affected by humoral factors is not significantly affected by nervous influences

The material presented in this chapter demonstrates the complexity of change in various parts of the circulatory system it serves to show how many different functions may be affected to produce a variety of syndromes which have previously been concealed under the cloak of 'shock or 'peripheral circulatory failure

REFERENCES

Surgical trauma

Barbour C M (1957) *Ann N Y Acad Sci* 66 844
Beecher H K (1949) *Resuscitation and Anesthesia for Wounded Men* Springfield Thomas
Bing R J (1951) *Bull N Y Acad Med* 27 407
— (1952) *Ann N Y Acad Sci* 55 367
Blalock A (1931) *Arch Surg Chicago* 22 314 598 610
Browne J S L (1945) In *Conference on metabolic aspects of bone and wound healing Proceedings of the Ninth Meeting New York N Y February 2–3 1945* Reifenstein E C Ed New York Josiah Macy Jr Foundation

Cameron G R and Courtice F C (1948) *Quart J exp Physiol* 34 165
— Allen J W Coles R F G and Rutland J P (1945) *J Path Bact* 57 37
Cannon W B and Bayliss W M (1919) In *Spec Rep Ser med Res Coun* No 26
Chambers R and Zweifach B W (1940) *J cell comp Physiol* 15 255
— — (1947) *Amer J Physiol* 150 239
Clarke R and Fisher M R (1956) *Brit J clin Pract* 10 746
Courtice F C (1946) *J Physiol* 104 321
— (1954) *Brit med Bull* 10 5
— and Korner P I (1952) *Aust J exp Biol med Sci* 30 511
Cuthbertson D P (1929) *Biochem J* 23 1328
— (1930) *Ibid* 24 1244
— (1954) *Brit med Bull* 10 33
Duncan G W and Blalock A (1942) *Ann Surg* 115 684
Eliel L P Pearson O H and White F C (1952) *J clin Invest* 31 119
Elkington J R and Winkler A W (1944) *J clin Invest* 23 93
Engel F L (1952) *Shock and Circulatory Stasis Transactions of the Second Conference* New York Josiah Macy Jr Foundation
Fine J (1953) *Shock and Circulatory Homeostasis Transactions of the Third Conference* New York Josiah Macy Jr Foundation
— Frank H Schweinburg F Jacob S and Gordon T (1952) *Ann N Y Acad Sci* 55 429
Firt P and Hejhal L (1957) *Lancet* 2 1132
Frank H A Jacob S W Schweinburg F B Goddard J and Fine J (1952) *Amer J Physiol* 168 430
Fulton J F (1955) *Textbook of Physiology* 17th ed Philadelphia and London Saunders
Gamble J L (1952) *Chemical Anatomy Physiology and Pathology of Extracellular Fluid* Cambridge Mass Harvard University Press
Gibson J C Seligman A M Peacock W C Fine J Aub J C and Evans R D (1947) *J clin Invest* 26 126
Gordon H L (1897) *Sir James Simpson* London T Fisher Unwin
Grant R T (1954) *Brit med Bull* 10 15
— and Reeve E B (1951) *Spec Rep Ser med Res Coun* No 277
de Groot J and Harris G W (1950) *J Physiol* 111 335
Heinermann H Smythe C and Marks P (1953) *Amer J Physiol* 174 352
Horton J A G and Davison M H A (1955) *Brit J Anaesth* 27 139
Howard J E Bigham R S Jr Eisenberg H Wagner D and Bailey E (1946) *Johns Hopk Hosp Bull* 78 282
Howard J M (1953) *Shock and Circulatory Homeostasis Transactions of the Third Conference* New York Josiah Macy Jr Foundation
Hume D M and Wittenstein G J (1950) In *Proceedings of the First Clinical ACTH Conference* Philadelphia Blakiston
Ingle D J Ward E O and Kuizenga M H (1947) *Amer J Physiol* 149 510
— Meeks R C and Thomas K E (1951) *Endocrinology* 49 703
Kark R M Chapman R C Consolazio C F and Nesby C (1952) *J Lab clin Med* 40 817
Knisely M H Barker S Bloch E H Lipscombe A Warner L Brooks F Dragstedt L R Schneider C L Le Quire V S Berrington Stoner H and Irwin J (1950) *Anat Rec* 106 209
Kohlstaedt K G and Page I H (1944) *Surgery* 16 430
Landis E M (1928) *Amer J Physiol* 83 528
Le Quesne L P and Lewis A A G (1953) *Lancet* 1 153
Mazur A and Shorr E J (1948) *J biol Chem* 176 771
McCance R A and Widdowson E M (1951) *Proc roy Soc* B138 115
McCann S M (1953) *Amer J Physiol* 175 13
Moon V H Morgan D R Lieber M M and McGrew D (1941) *J Amer med Ass* 117 1
Moore F D (1953) *Ann Surg* 137 289
— and Ball M R (1952) *The Metabolic Response to Surgery* Springfield Thomas
Opdyke D F and Foreman R C (1947) *Amer J Physiol* 148 726
Porter R W (1952) *Amer J Physiol* 169 629

Raventós J (1936) *Brit J Pharmacol* 11 394
Reeve E B Nanson E M and Rundle F F (1951) *Clin Sci* 10 65
Shorr E Zweifach B W and Furchgott R F (1945) *Science* 102 489
— — — and Baez S (1947) *Trans Ass Amer Phycns* 60 28
Starling E (1918) *The Law of the Heart* New York Longmans Green
Swingle W W Remington J W Drill V A and Kleinberg W (1942) *Amer J Physiol* 138 156
Wiggers C J (1947) *Amer Heart J* 33 633
— (1950) *Physiology of Shock* New York The Commonwealth Fund
Wilkinson A W Billing B H Nagy G and Stewart C P (1950) *Lancet* 2 135
Zweifach B W (1936) *Amer J Anat* 60 473
— (1951) *Transactions of the First Conference on Shock and Circulatory Homeostasis* New York Josiah Macy Jr Foundation

Anaesthesia and the circulation

Abramson D I Grollman A I and Schwartz A L (1941) *Anesthesiology* 2 186
Altschule M D (1954) *Physiology in Diseases of the Heart and Lungs* Harvard University Monograph No 10
Bain W A and Broadbent J L (1949) *Brit med J* 1 1137
Barcroft H Edholm O G McMichael J and Sharpey Schafer E P (1949) *Lancet* 1 489
Bayliss L E and Brown A (1940) *J Physiol* 98 190
Beecher H K (1946) *Anesthesiology* 7 644
— (1949) *Resuscitation and Anesthesia for Wounded Men* Springfield Thomas
— and Todd D P (1954) *Ann Surg* 140 2
Bencini A and Parola P L (1956) *Surgery* 39 375
Brown E B Jr and Millar F (1952) *Amer J Physiol* 169 56
Brown P A I and Sellick B A (1955) *Brit med Bull* 11 174
Clutton Brock J (1949) *Brit med J* 1 1007
Crafoord C (1938) *Acta chir scand Suppl* 54
Dripps R D (1947) *Anesthesiology* 8 15
Editorial (1957) *Anesthesiology* 18 126
Edwards G Morton H J V Pask E A and Wylie W D (1956) *Anaesthesia* 11 194
Etsten B E Rheinlander H F Reynolds R N and Li T H (1953) *Surg Forum* 4 649
Foster C A O Mullane E J Gaskell P and Churchill Davidson H C (1954) *Lancet* 1 614
Grant R T and Reeve E B (1951) *Spec Rep Ser med Res Coun* No 277
Gray T C (1957) *Lancet* 1 383
— and Gregory R A (1948) *Anaesthesia* 3 17
Green J H (1955) *J Physiol* 130 37
Griffith H R and Johnson J E (1942) *Anesthesiology* 3 418
Grimson K S (1949) *Factors Regulating Blood Pressure Transactions of the Third Conference* New York Josiah Macy Jr Foundation
Halford F J (1943) *Anesthesiology* 4 67
Hamilton W F Moore J W Kinsman J M and Spurling R G (1932) *Amer J Physiol* 99 534
Harbord R P (1947) *Proc R Soc Med* 40 172
— (1950) *Ibid* 43 372
— (1955) *Proceedings World Congress of Anesthesiologists* Minneapolis Burgess
Hershey S G Zweifach B W and Rovenstine E A (1953) *Anesthesiology* 14 245
Hill M (1949) *Brit med J* 2 601
Hunter A R (1953) *Brit med J* 1 640
Johnson S R (1951) *Acta chir scand Suppl* 158
Johnstone M (1950) *Brit Heart J* 3 239
— (1956) *Brit J Anaesth* 28 392
Kitchin A H Sanger C de Wardener H E and Young M I (1953) *Clin Sci* 12 361
Leatham A Cook P and Davies J G (1956) *Lancet* 2 1185
de Lee J G Churchill Davidson H Miles B E and de Wardener H E (1953) *Clin Sci* 12 169
Lequime J (1940) *Acta med scand Suppl* 107

Li T H and Etsten B E (1957) *Anesthesiology* 18 15
— (In Press)
Lynn R B and Shackman R (1951) *Brit med J* 2 333
— Sancetta, S M Simeone F P and Scott R W (1952) *Surgery* 32 195
Macintosh R R (1949) *Brit med J* 1 852
McMillan I K R Cockett F B and Styles P (1952) *Thorax* 7 205
Meek W J (1940) *Proc Mayo Clin* 15 237
Melrose D G (1955) *J Physiol* 127 51
— Dreyer B Bentall H H and Baker J B E (1955) *Lancet* 2 21
Miles B E and de Wardener H E (1952) *J Physiol* 118 140
Milstein B B (1956) *Ann roy Coll Surg Engl*, 19 69
Morris L E Noltensmeyer M H and White J M Jr (1953) *Anesthesiology* 14 153
Nickerson M (1949) *J Pharmacol* 95 27
Organe G S W (1950) *Proc R Soc Med* 43 181
Price H L (1951) *J clin Invest* 30 1243
— (1953) *Anesthesiology* 14 1
Prime F J and Gray T C (1952) *Brit J Anaesth* 24 101
Pugh L G C and Wyndham C L (1950) *Clin Sci* 9 189
Raventos J (1956) *Brit J Pharmacol* 11 394
Robertson J D and Swan A A B (1957) *Quart J exp Physiol* 42 113
— — and Whitteridge D (1956) *J Physiol* 131 463
Sarnoff S J (1955) *Physiol Rev* 35 107
Scherf D Goldfarb M and Bussan R (1955) *Circulation* 12 271
Shackman R and Graber I G (1952) *Brit med J* 1 1284
— — and Melrose D G (1953) *Clin Sci* 12 307
— — and Redwood C (1951) *Clin Sci* 10 219
— Wood Smith F G Graber I G Melrose D G and Lynn R B (1954) *Lancet* 2 617
Stewart H J Deitrick J E Crane N F and Thompson W P (1938) *J clin Invest* 17 449
Thomas E T (1957) *Lancet* 2 772
Wardener de H E Miles B E de Lee J G Churchill Davidson H Wylie D and Sharpey Schafer E P (1953) *Clin Sci* 12 175
Wechter R L Dripps R D and Kety S S (1951) *Anesthesiology* 12 308
Wylie W D (1956) *Brit J Anaesth* 28 551
Zoll P M (1952) *New Engl J Med* 247 768

CHAPTER 9

HYPOTHERMIA

T. CECIL GRAY

NO VOLUME reviewing modern trends in anaesthesia would be complete without some reference to hypothermia, which at least in theory promised to be one of the most exciting advances in anaesthesia and surgery of the last decade. Since its use by McQuiston (1950) to improve the oxygenation of 'blue babies', the development of hypothermia for heart surgery and in other fields has been rapid. Sufficient time has passed to permit some assessment to be made of the place that this technique may occupy in surgical and anaesthetic techniques. It is the purpose of this chapter to discuss this procedure under the headings of (1) its purpose, (2) the methods of achieving it, (3) its hazards and, (4) its indications.

THE PURPOSE OF HYPOTHERMIA

Whatever may be its indications, the principle underlying the use of hypothermia is the reduction in metabolism and, therefore, in oxygen uptake which is associated with a fall in body temperature in warm blooded animals. Whether this fall in oxygen uptake bears a near relationship to the temperature, as maintained by Bigelow and his colleagues (1950), or is exponential as suggested by Spurr, Hutt and Horvath (1954) may have little practical relevance at present, although if it becomes feasible to use in humans the lower degrees of temperature which have been achieved in animals, this point may come to have some significance. Certainly, if the relationship is not linear it may not be true to consider that at 10° C the oxygen uptake will be zero, as postulated by Lynn and his co-workers (1954). In dogs Bigelow and his colleagues (1950) found that at 30° C the oxygen uptake is reduced approximately by 50 per cent, and at 25° C by 65 per cent. It is clear that under such conditions the time for which the brain or any other vital organ can survive when deprived, either wholly or in part, of its oxygen supply will be considerably increased.

Two points, however, arise which may prove of importance.

Relation between oxygen uptake and cellular requirements

The reduction in oxygen uptake is not necessarily the same as the reduction in oxygen requirement by the cells. The facility of aerobic metabolism may be reduced by interference with enzymic action. There is, moreover, at low temperatures an interference with the dissociation of oxyhaemoglobin. The dissociation curve is shifted to the left, so that the oxygen is less readily released to the tissues.

Variation in reduced oxygen consumption for different organs

Secondly, the reduction in oxygen consumption is not the same for each organ

throughout the body It has been shown that whereas the general oxygen uptake by the body at 26–27° C is 40 per cent of normal, that by the heart is reduced only by 50 per cent As the work done by the heart at this lower temperature is little less than at normal temperatures, this maintenance of oxygen usage may prove some protection against myocardial hypoxia (Edwards and his colleagues 1954) Interesting work on monkeys by Bering and his associates (1956) indicated that the cerebral oxygen uptake showed little change as the temperature was lowered until a temperature of 31° C was reached, and then it dropped sharply, *reaching at approximately 27° C a value of 0 8–1 0 millilitre per 100 grammes of* brain compared with the normal 2 5–4 7 millilitres per 100 grammes of brain—a drop of about 25 per cent in 4° C As cooling proceeded the oxygen consumption continued to fall but only slowly So far as the brain was concerned the relationship of oxygen consumption to temperature was not linear but S shaped (Fig 16) These workers suggested that there was little to be gained by cooling much below

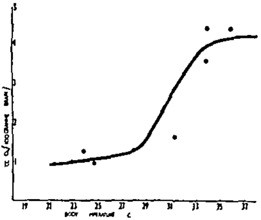

Fig 16 —Relation of oxygen uptake by the brain to temperature

(After Bering and his colleagues (1956) by courtesy of the authors and publishers)

30 C and certainly nothing below 27 C when the hazard of serious cardiac arrhythmias became considerable Earlier work (McMurrey and his colleagues, 1956) had shown that in monkeys electroencephalographic activity ceased after one minute of complete cerebral anoxia regardless of the temperature of the animals but that this condition was tolerated for 15 minutes at temperatures between 23 and 26 C (This must be compared with the finding of Lougheed and his colleagues (1955) that electroencephalographic activity ceased only after 25 minutes of brain anoxia at 23 5 C in dogs) However McMurrey and his colleagues (1956) found that in two dogs at a still lower temperature (22° C) complete cerebral anoxia for 15 minutes was not followed by recovery Repeated periods of anoxia each of 15 minutes resulted in cerebral damage in 3 out of 5 monkeys in the 26–23 C range but multiple periods of 12 minutes were tolerated These experiments serve as valuable indications of the times for which cerebral anoxia might be permitted in humans It is noteworthy, however, that Kimoto, Sugie and Asano (1956), using a technique of differential brain cooling, which will be described later, found that brain temperatures of the order of 16 C were well tolerated and permitted periods of complete circulatory occlusion considerably longer than those described above

Other organs for example the kidney, are also protected to some extent from ischaemic damage by hypothermia (Mayer and his colleagues, 1957)

Severe hypothermia

With the aim of reducing oxygen need practically to zero, the possibility of submitting warm blooded animals to more drastic hypothermia has been explored and it has been found possible to cool small animals to 0° C and even lower with recovery Andjus (1951) found that 20 per cent of rats recovered after cooling to temperatures just above 0° C and more recently he and his colleagues (Andjus and Smith 1955 Andjus and Lovelock 1955) have obtained 75-100 per cent recovery in these animals after cooling to temperatures just above freezing point and after cardiac and respiratory arrest for one hour Golden hamsters were even more tolerant of cooling and could be kept on ice with circulatory arrest for up to seven hours (Smith, 1956) and survived supercooling to −5° or −6° C Even dogs have survived cooling to 1 5° C when the circulation has been maintained with a simple pump and oxygenator (Gollan and his co workers, 1955) The fact that the rats maintained in circulatory arrest for one hour showed no apparent alteration in behaviour or memory (Andjus and his colleagues 1955) suggests that the achievement of zero oxygen consumption with recovery is attainable in warm blooded animals

Whether these remarkable results will ever have any clinical application is highly speculative, but they will undoubtedly stimulate investigation into the feasibility of using temperatures considerably lower than hitherto

Shivering and its control

As long ago as 1876 Claude Bernard appreciated that shivering enormously increased the metabolism and was an important mechanism protecting the organism against exposure to cold Shivering is a response to an increased temperature gradient between the receptor organs for cold sensation in the skin and centres in the hypothalamus (Davis and Mayer, 1955) Not only visible shivering but also a general hypertonicity of the skeletal muscles which may precede or supersede shivering results in increased metabolic, heart and respiratory rates This protective reflex must be controlled if the hypothermic state is to be achieved without harm and with reasonable speed Shivering is prevented by deep anaesthesia (Bigelow and his colleagues, 1950), or by sedation or light anaesthesia together with either curarization (originally suggested by Krogh in 1916) or chlorpromazine Chlor promazine is the principal effective agent in this respect in the mixture of sedative drugs recommended by French workers and exerts its effect through both a peripheral action on the muscle fibre and also probably on the hypothalamic temperature controlling centres

The importance of invisible shivering has been stressed by Brom (1957) who suggested that it is indicated by an increase in serum potassium concentration in the absence of other explanation and takes this as an indication for more relaxant

METHODS OF ACHIEVING HYPOTHERMIA

Before describing the methods which are used in clinical practice to achieve hypothermia, attention must be drawn to the difficulty of measuring body tempera ture Body *temperature* is in fact, a meaningless term, for it will vary with the

part of the body where it is measured There is obviously a difference in temperature between the skin and the interior of the body, but it has been shown that there is no uniformity of temperature in the central body core nor even in the various internal organs (Horvath Rubin and Faltz, 1950) Such differences will not necessarily disappear with cooling, but may in fact be increased if cooling is induced by perfusion of cooled blood primarily through the heart or brain Lucas (1956) points out that the rectal temperature used by many workers may give dangerously misleading results In clinical work, it is the temperatures of the brain and of the heart which are of prime importance and these are probably best measured by thermometers, electrical or mercurial, inserted in the pharynx or mid oesophagus To obtain a more accurate measurement of brain temperature Kimoto, Sugie and Asano (1956) used a needle electrode thermometer inserted into the jugular vein but in their work cooled blood was being circulated primarily through the brain and it is doubtful whether jugular vein blood was indicative of true brain temperatures Similarly it must be remembered that if cold blood is being introduced directly into the heart as in the vein to vein method of extra corporeal cooling that organ will cool more rapidly than other parts of the body

The methods of cooling may be classified under three headings (1) surface cooling, (2) body cavity cooling and (3) extracorporeal cooling

Surface cooling

The application to the unprotected surface of the body of ice packs, or of a mattress through which iced water may be circulated, or the total immersion of the body in iced water, are simple and effective methods of lowering the temperature The two protective reflexes shivering and vasoconstriction must be controlled

If vasoconstriction is permitted there will be delay in the fall of temperature and also a danger of tissue damage (frostbite) When the skin is in contact with temperatures around 0 C the initial reaction is vasoconstriction, but this may give place to vasodilatation It is however, not necessarily the case that the vasodilatation results in adequate capillary perfusion as it is probable that arteriovenous connections open up (Lewis, 1930) If vasoconstriction is permitted only a relatively small volume of blood will perfuse the cold surface tissues and cooling will be largely by conduction from the skin inwards There will, therefore, be a gradient of temperature from the surface to the central core of the body Two undesirable effects follow If active cooling is stopped at what is considered the desired temperature the warm blood from the interior will continue to perfuse the cold surface tissues and there will be a continued fall in temperature of the internal organs A further effect will be that during rewarming the vasoconstriction will give place to vasodilatation which will result in a considerable increase in the capacity of the vascular bed to accommodate blood This combined with the reduction in plasma volume which occurs in these circumstances as early investigators discovered may result in severe and possibly fatal peripheral circulatory failure (Dill and Forbes 1941)

Shivering and vasoconstriction must, therefore be controlled and fortunately the drugs which affect the one reaction generally modify the other Virtue (1955) used anaesthesia induced with thiopentone and cyclopropane and maintained with ether, with the addition if shivering occurs of a muscle relaxant With the

exception of the head and neck he immerses the patient completely in a bath of iced water The lungs are hyperventilated throughout with the aim of maintaining a blood pH on the alkaline side of normal in order to reduce the risk of serious cardiac arrhythmia The need for anaesthetic ceases at 28° C and ventilation is thereafter with oxygen only Others (Gray, 1955, Burrows and his colleagues 1956) have preferred lighter anaesthesia supplemented with chlorpromazine Chlorpromazine, 100 milligrams, is given orally the night before operation and 50 milligrams intramuscularly one and a half hours before cooling Light anaesthesia is induced with a small dose of thiopentone and maintained with nitrous oxide and oxygen only A short acting relaxant may be used for intubation Curarization is used when abdominal relaxation is required or during thoracotomy to achieve control of the respiration and at the end of the procedure it is reversed in the usual manner, with neostigmine In the absence of curarization shivering is controlled if necessary, by further intravenous injection of chlorpromazine (10–25 milligrams) and/or analgesics such as methorphinan (0 5–1 5 milligram) or pethidine (20–50 milligrams) Cooling is achieved by the application back and front, of ice packs, or by the use of a cooling mattress Unless there is profound respiratory depression or relaxants have been used the respirations are not assisted by these workers

Even when full vasodilatation is maintained, some allowance must be made for a fall in temperature after active cooling has been stopped This after drop ' of temperature will be greatest in the well-covered patient as fat is an excellent thermal insulator, such patients will also tend to cool more slowly than will the thin individuals who cool rapidly and show little or no after drop Children are particularly unpredictable They cool rapidly and also may continue to drop in temperature Virtue (1955) has recommended that active cooling should usually be stopped when two thirds of the desired fall in temperature has been achieved This is good advice to the tyro who wishes to avoid trouble With experience however, if the build of the patient is borne in mind it is possible to predict reasonably accurately the after fall of temperature and to achieve a desired stable level of temperature It may be helpful to change the posture of the patient during the cooling to avoid pooling of cold blood and its subsequent re entry into the general circulation (Burrows and his colleagues 1956)

A disadvantage of surface cooling is the danger of the onset of fibrillation during the cooling process and before the chest is opened Brom (1957) of Leiden suggests in critical cases such as severe aortic or pulmonary stenosis an endotracheal tube should be passed before anaesthesia commences, anaesthesia then induced and the chest opened Cooling is then carried out in a bath with the chest open so that measures for defibrillation can be taken without delay Brom also stressed the importance of hyperventilation with close pH control and as has been stated above with control of the serum potassium concentration

Rewarming presents no difficulty except that of speed Covering with blankets and perhaps the cautious use of a gentle heat cradle outside the blankets, together with the natural recovery processes when the anaesthesia is stopped restore the temperature to normal The time taken for rewarming may be as long as six hours and this is an undoubted disadvantage of the method when more rapid rewarming is required, as perhaps after an incident of severe cardiac irregularity during heart surgery Efforts to overcome this by the use of diathermy coils

wrapped round the abdomen of the patient as described by Virtue (1955) or by radiofrequency treatment (Bigelow, Hopps and Callaghan, 1952) have not proved satisfactory, as the danger of burns is very real and limits the speed at which the rewarming process may be carried out. Obviously the use of warm water baths is more rapid (Sellick, 1957) but in an emergency this is precluded by the open chest. Brom, in fact, rewarms the patient in a bath with the chest still open if there is any anxiety as to the condition of the heart. The pouring of large volumes of warm saline into the thoracic cavity (Blades and Pierpoint, 1954) is not particularly efficient and is extremely cumbersome to carry out. When temperatures below 29° C are not being employed and there is no manipulation of the heart so that ventricular fibrillation is not likely, this disadvantage of surface cooling is of little importance.

Body cavity cooling

Blades and Pierpoint (1954) described a method of cooling and rewarming a patient by pouring cool and warm saline solution respectively into the open thoracic cavity. The method is slow and requires large volumes (as much as 75 litres) of saline solution and does not appear to be very practicable. Furthermore, during cooling the heart is exposed directly to the cold saline solution and cardiac irregularities are common. In one patient cooling had to be stopped on no less than nine occasions because of arrhythmia. Khalil and MacKeith (1954) found intragastric cooling useful in rabbits and applied it in one patient, a child suffering from hyperthermia. The apparatus consisted of a piece of thin portex tubing at the end of which was a balloon made of a finger stall which would inflate to hold 250 millilitres. After the balloon had been introduced into the stomach it was inflated with ice cold water and left *in situ* for about two minutes. Repeated fillings of the balloon are required and extrasystoles were not uncommon during the cooling, especially in the early stages. The advantages suggested are controllability, lack of tissue gradients and early cooling of vascular organs with high metabolic rates such as the liver. The method, however, is slow and not likely to replace surface or extracorporeal cooling, although it might be found useful where, during surface cooling, all efforts must be made to warm quickly.

Extracorporeal cooling

The method of allowing blood to pass from a cannulated artery through tubing immersed in a cooling medium and returning it to a vein was first described by Boerema and his colleagues (1951) and Delorme (1952). This procedure was modified by Ross (1954) who suggested the withdrawal of blood from a vein and by Brock (1956) who used cannulae inserted through the right auricular appendage —one up in the superior vena cava and the other down in the inferior vena cava. This method of veno-venous cooling requires a pump to withdraw the blood from the vein and move it round the cooling coil and so back to the return cannula. It has the advantage of avoiding cannulation of a major artery and it does not entail the creation of artificial arteriovenous fistulae which in patients with congenital heart anomalies can so upset the circulatory dynamics as to be dangerous. However, circulating blood through tubing and a pump is likely to cause haemolysis and also interfere with the clotting mechanism. Obviously, the more often the blood has to pass through the apparatus the more severe are these effects.

likely to be, so the cooling must be efficient and fairly rapid—but here again a balance must be struck for, if it is too rapid the temperature of the heart, which is the first organ by this method to be exposed to the cold blood, may drop too quickly and too far and cardiac arrhythmia of a serious nature may result Brock suggests a cooling rate of 1° C each five minutes The cooling plant may be a complex refrigerating and rewarming plant as used by Brock (1956) or it may be extremely simple as is that used by Lucas (1956) The latter consists of a coil of portex tubing of 4 millimetre bore and 16 feet long inserted in a 3 lb Kilner jar filled with a mixture of Cardice (carbon dioxide snow), saline and alcohol The proportion of alcohol determines the freezing point of the mixture and the temperature of the fluid should be around −2° C Lucas also suggests for rewarming the use of molten sodium thiosulphate which melts

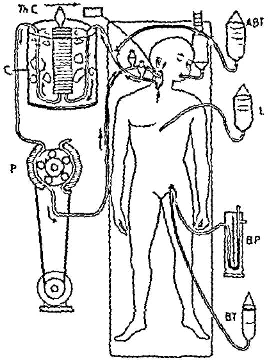

FIG 17 —Scheme for selective brain cooling by irrigation

Th C Thermocouple into internal jugular vein
P Pump of DeBakey type
A B T Arterial blood transfusion
I Irrigation with saline solution into the incised heart cavity
B P Blood pressure of femoral artery
B T Blood transfusion to femoral vein

(After Kimoto Sugie and Asano (1956) by courtesy of the authors and publishers)

at 46° C but warm water maintained at about that temperature is quite satisfactory The output from the cooling coil should be of the order of 100 millilitres per minute

Parkins Jensen and Vars (1954) used extracorporeal cooling to lower the brain temperature considerably below that of the general body temperature, and Kimoto Sugie and Asano (1956) have developed this experimental approach on dogs, and applied the technique clinically in 11 patients A further 25 cases with 2 deaths have been treated in this way (Kimoto and his colleagues 1957) These workers cannulate the carotid artery with polythene tubes so that the blood can be passed through a cooling coil and returned to the distal side of the cannulated artery (Fig 17) Using this technique the brain temperature as measured by the temperature of jugular vein blood was lowered to 14 C while the general body temperature was as high as 31 or 32 C Doubt may be expressed as to how far

jugular vein blood reflects actual brain temperature As the temperature of the heart is above the critical level below which ventricular fibrillation is always a hazard the advantage of this procedure is clear The early clinical work by these workers is encouraging, but it must be remembered that the spinal cord will be nearer to the general body temperature than to that of the brain Moreover, the danger of carotid artery thrombosis is considerable although Kimoto (1957) states that this complication has not been experienced in his series and suggests that it can be prevented by the administration of heparin

The method of extracorporeal cooling has obvious advantages It permits the surgeon to open the chest and explore the cardiac anomaly under normothermic conditions when heart irritability is not increased, and measure the various intra cardiac pressures which may assist in the diagnosis (Ross, 1957) It also provides the best possible control over the temperature in that rewarming can be carried out efficiently and speedily and after drop of temperature does not occur Obviously the method of vein to vein cooling using the venae cavae, is unsuitable for extrathoracic operations It is, indeed, doubtful whether cannulation of a major vessel is justified ever for such procedures when the surface cooling method has proved so satisfactory The circulation of blood through tubing and a pump carries its own hazards of interference with coagulation, a complication which has been not infrequently experienced with this technique and which will be discussed more fully under hazards

HAZARDS OF HYPOTHERMIA

It should be remembered that hypothermic anaesthesia carries all the hazards of general anaesthesia The patient for example, who is being cooled is just as likely to regurgitate stomach contents as is any other anaesthetized patient and the regurgitated material is just as likely to be aspirated in the absence of intubation with a cuffed tube Such a case during the induction of hypothermia has been described (Dundee Gray Mesham and Scott, 1953) However this procedure also carries its own dangers and these may be grouped under (1) the circulatory system (2) skin and internal organs and (3) the metabolism

The circulatory system

Blood pressure

The blood pressure falls during hypothermia as a result of the fall in cardiac output and the vasodilatation which ensues as a result of the administration of vasodilating drugs or of the low temperature The fall in blood pressure is not often very pronounced and, in fact, when extreme hypotension is desired as during highly vascular neurosurgical operations a hypotensive drug may have to be used (Burrows and his colleagues 1956) Severe falls in blood pressure can occur however and if there is a cardiac deficiency the adequacy of the perfusion of the coronary arteries must always be borne in mind

Cardiac arrhythmia

A fall in heart rate is a normal accompaniment of cooling in the absence of shivering It is due to depression both of the SA node and of conduction through the bundle of His Electrocardiograms at low temperatures show that cardiac

systole takes up a greater than normal fraction of the cycle and below 30 C these conduction changes are likely to be manifested by a prolonged PR interval spreading of the QRS complex and lengthening of the ST interval ST deviations from the isoelectric line are not uncommon (Scurr 1955) Auricular fibrillation is not infrequently seen during hypothermia in clinical practice

Cookson and Di Palma (1955) found that a cardiac crisis occurred in dogs cooled to temperatures between 23 and 15 C This was manifested by the cessation of sinus rhythm the onset of nodal rhythm of intense bradycardia ventricular fibrillation or more rarely of heart block or sinus tachycardia It appeared that ventricular extrasystoles heralded the ventricular fibrillation and a shifting pace-maker the bradycardia The bradycardia was not relieved by atropine or vagotomy It is interesting that an intense bradycardia unrelieved by atropine has been seen in clinical practice (Dundee cited by Gray, 1957) It is however the danger of ventricular fibrillation which has dogged the use of this technique and its fullest exploitation A great deal of research has been directed towards the elucidation of the cause of this arrhythmia and its prevention In order to obtain a clearer picture of the trends in opinion it is necessary to distinguish between what is generally regarded as factual—accepted opinion—and a number of other observations linked together by varying hypotheses It is a fact that although ventricular fibrillation may occur at any temperature, it is very much more likely when the temperature of the heart muscle is below 29 C and when there is actual manipulation of the heart This is born out by the report of a series of over 180 neurosurgical operations under hypothermia without one case of ventricular fibrillation (Gray 1957) A second generally accepted observation is that it is much less likely to be seen in the young animal than in the adult (Adolph 1951) To these might be added but perhaps with less evidence a widely held opinion that the abnormal myocardium such as that damaged by rheumatic disease or by gross hypertrophy is more prone to fibrillate Apart from these agreed opinions different workers have laid emphasis on many differing observations as the principal aetiological factor Thus it has been attributed to hypocarbia (Bigelow and his colleagues 1950) hypercarbia (Fleming 1954 Lynn and his colleagues 1954 Swan and his colleagues 1953b) hyperkalaemia (Sealy Young and Harris 1954) hypokalaemia (Zeavin Virtue and Swan 1954) too much calcium (Melrose 1954) and too little calcium (Swan and his colleagues 1953a) These varying observations appear to be condensing into two opinions One lays emphasis on the influence of changes in the hydrogen ion concentration which occur during hypothermia and the other attributes the increased cardiac irritability at low temperatures to myocardial hypoxia A brief summary of the principal evidence for these two views may clarify the present position

From the earliest days of work on the use of hypothermia for cardiac surgery Bigelow has stressed the importance of maintaining a steady level of pH in hypothermic patients (Bigelow and his co-workers 1950) Sudden changes in the reaction of the blood would appear to predispose to ventricular fibrillation However shortly after Bigelow s work Cookson Neptune and Bailey (1952) showed that the survival rate in cooled dogs was improved by pulmonary hyperventilation and this was confirmed by the work of Osborne (1953) and Swan and his colleagues (1953b) Fundamental work has been done by Brooks and his colleagues (1955) on the excitability of the heart Although they demonstrated the greatly increased

absolute refractory period at low temperatures, they were unable to show any definite increase in the irritability of the myocardium Although Covino and Williams (1955) originally claimed to have demonstrated alterations in the threshold of the myocardium resulting from acidosis, a later communication (Hegnauer and Covino, 1956) drew attention to the inadequacy of the technique which they employed and appeared to indicate that there were relatively slight deviations from the normal under these circumstances

It may be that the earlier observations suggesting that a sudden *change* in pH is an important precipitatory factor will prove valid Certainly this is borne out by the fact that this complication is not infrequently initiated in clinical practice when the clamps which have been occluding the venae cavae during cardiac surgery are removed Brewin and his colleagues (1955) have shown that circulatory occlusion during hypothermia results in a marked metabolic acidosis due to lactacidaemia and when the clamps are removed blood with a very low pH immediately enters the heart It may well be that part of the protection afforded by the lengthy hyperventilation suggested by Swan (Swan and his colleagues 1953a Swan and Zeavin 1954) is attributable to the fact that the resulting respiratory alkalosis will tend to offset this metabolic acidosis The lactacidaemia can also be prevented by the prevention of congestion in the inferior cava during occlusion by withdrawing the blood

Those who hold the opinion that myocardial hypoxia is the fundamental cause of ventricular fibrillation have also considerable experimental support for their view The effect of cooling on the dissociation curve of oxyhaemoglobin results in less ready dissociation of the oxygen from haemoglobin (Fig 18) and there is the possibility of tissue hypoxia without anoxaemia This effect is further increased by any hyperventilation of the lungs which results in hypocarbia Bigelow and others strive to avoid this by ventilation with 5 per cent carbon dioxide (Bigelow and his colleagues 1950, Niazi and Lewis 1955) Against this view is the fact that there is no change in the AV oxygen difference in the blood passing through the coronary arterial system as the temperature is reduced (Penrod 1951) and apparently the heart can take up as much oxygen from the blood at 24° C as at normal body temperature (Swan, 1954) There is, however, evidence that the coronary blood flow is greatly reduced during hypothermia and Edwards and his colleagues (1954) have used the nitrous oxide desaturation technique to demonstrate this At the same time they measured the oxygen uptake and work done by the left ventricle At temperatures of 27 –25 C the coronary blood flow was reduced as also was the work done by the ventricle but a decreased efficiency of the ventricle was indicated by the fact that the drop in ventricular work was greater than the drop in oxygen uptake These workers considered that there was during hypothermia an impairment in the ability of the myocardium to convert aerobic energy into useful work It is suggestive of myocardial hypoxia that just before the onset of ventricular fibrillation there is always a high serum potassium level in the coronary venous blood without a corresponding change in the arterial serum potassium Movement of potassium out of cells is characteristic of hypoxia Smith (1956) found that in six of nine dogs the coronary vein serum potassium was 20–30 per cent higher than was the arterial just immediately prior to the commencement of fibrillation and that this was associated with electrocardiographic changes characteristic of myocardial hypoxia Moreover these electrocardiograph

effects could be used to predict the onset of serious arrhythmia Smith also confirmed the findings of others (Gollan and his colleagues, 1955) that full coronary perfusion with oxygenated blood during hypothermia restored the electrocardiogram to normal and prevented fibrillation It could be regarded as further evidence

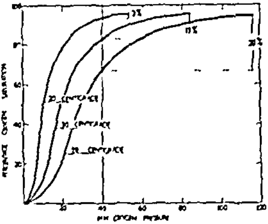

Fig 18.—Dissociation curve of oxyhaemoglobin as related to temperature
(After Blades and Pierpont (1954) by courtesy of the authors and publishers)

that hypoxia is a factor in the cause of ventricular fibrillation that defibrillation is much more likely to be successful in the heart which is well oxygenated

It seems likely that both factors, acidaemia and myocardial hypoxia, predispose to this complication and the truth is that, in the words of Boerema 'it is not one deviation alone for instance the change in the *p*H of the blood, which brings danger in its wake but rather the loss of a harmony and the dissociation of normal life processes, which cause death to occur ' (Boerema and his colleagues, 1956)

Apart from ventilatory adjustments and coronary perfusion several prophylactic measures have been suggested which it is claimed by their various advocates, reduce the incidence of ventricular fibrillation Infiltration of the superior atriocaval junction (SA node) with procaine appeared to prevent fibrillation in 20 dogs submitted to ventriculotomy under hypothermia whereas fibrillation occurred in 90 per cent of control dogs undergoing the same procedure (Radigan Lombardo and Morrow 1956 *see also* Riberi, Siderys and Shumacker 1956) Prevedel Montgomery and Swan (1954) suggested the injection of neostigmine into the base of the aorta, and found experimentally that this procedure gave some protection However, the dose of neostigmine required for full protection is such as to slow the heart to about 20–25 beats per minute and the danger of complete cardiac arrest is considerable (Montgomery Prevedel and Swan, 1954) The use of neostigmine injections clinically has been found useful in some centres and doses of 0 25–0 5 milligram are injected intravenously by Virtue (1955) when the required temperature has been reached and 0 03 milligram per stone body weight are injected by Sellick (1957) just proximal to the aortic clamp before cardiotomy Not surprisingly acetylcholine (50–80 milligrams in dogs) has been reported as having a similar action (Kimoto Sugie and Asano 1956) Several drugs have been investigated for their effect on ventricular fibrillation but the most promising is a report on Ambonestyl (2 diethylaminoethyl isonicotinamide) which reduced the incidence of ventricular fibrillation during ventriculotomy in acidotic dogs at 25 –23 C from 80 per cent to 30 per cent Combining the administration of this substance with hyperventilation reduced the incidence by 100 per cent (Covino

and Hegnauer, 1956) Quinidine sulphate (30–40 milligrams per kilogram body weight) has also been reported as affording some protection (Gollan and his colleagues, 1955)

If ventricular fibrillation does occur the treatment has become standardized The original remedy in which the fibrillation was converted to asystole by the injection of potassium chloride into the coronary circulation and then a rhythmic beat restored by massage (Swan and Zeavin, 1954) has been superseded by the use of an electric shock, which not infrequently restores normal rhythm without initial asystole Electrical defibrillation is likely to be more effective if the heart is not flabby and soft and if the myocardium is reasonably well oxygenated The intracardiac injection of 1–3 millilitres of 1 3000 adrenaline (1 1000 solution has been used with success) will tighten up a flabby myocardium and cardiac massage will ensure adequate myocardial oxygenation To deliver the shock the electrodes should be placed across the heart from the base to the anterior surface and the current used should be of 1 5–2 amps at a voltage of 120–200 volts with a duration of 0 1 second The shock may be repeated if necessary until asystole or normal rhythm is restored

The blood

The blood increases in viscosity as the temperature falls but more important in practice has been the alteration in the coagulation characteristics This is not just a matter of the slowing in coagulation which is seen *in vitro* at low temperatures During hypothermia there is a fall in the number of platelets which it is generally accepted is likely to be greater when the extracorporeal method is used Helmsworth and Cole (1956) claim to have shown that both the fall in platelets and the other blood changes, namely haemoconcentration and reductions in the eosinophil and leucocyte counts, as well as in the mean corpuscular haemoglobin concentration are, in fact, greater when animals are cooled by the surface method It may be of significance however, that the animals cooled by the extracorporeal method in this work were on an average at a temperature 5° C higher than those to which surface cooling was applied Animals cooled by the surface method and maintained at a low temperature (about 29° C) for days may show a progressive slowing of coagulation time (hair capillary method), loss of fibrinogen and reduced platelet counts until after three days the coagulation time of their blood may be upwards of half an hour (Gray, 1957 Fisher and his colleagues, 1957) It is suspected but not yet established that this is associated with the release of some anticoagulant substance Intractable haemorrhage has not been a serious danger in patients cooled by the surface method but where there is a pre operative clotting deficiency as in liver cirrhosis, this has proved a real and fatal complication (Dundee Gray Mesham and Scott 1953) Much more difficulty with clotting has however been experienced following extracorporeal cooling The circulation of blood through plastic tubes and a pump is responsible and this complication is particularly likely to be seen if the blood has to be circulated through the apparatus over a prolonged time during cooling and rewarming In adults the rate of cooling suggested by Brock (1956) of one degree change of temperature every five minutes should be achieved if this danger is to be avoided If intractable bleeding is experienced the best treatment is transfusion with fresh heparinized blood followed by an adequate dose of protamine sulphate

Skin and other organs

The effects of extreme cold on living cells has been well reviewed by Burton and Edholm (1955) but this would seem to have little immediate practical importance to those practising hypothermia Future vistas may be opened out perhaps, by the many reports of the possibility of cooling warm blooded mammals to temperatures around 0° C (Smith, 1956 Gollan and his colleagues, 1955) The practical point, however, is that there is a real danger of producing frostbite during surface cooling unless adequate vasodilatation is maintained (Gray, 1955, Sellick, 1957)

There has been some discussion of the effects of hypothermia on the liver and other parenchymatous organs Knocker (1955) demonstrated severe damage to the liver kidneys and adrenal glands in dogs which had been made hypothermic by surface cooling and drew attention to the similarity of these changes to the stress responses reported by Selye (1946) These occurred only after hours of maintenance at temperatures around 25° C Other workers have not been able to reproduce these results after such short periods of cooling, but a recent report seems to indicate that similar changes may be found after days of hypothermia (Gray, 1957) It is not the general opinion that fear of such changes need contraindicate the use of hypothermia in clinical practice where it is indicated

The metabolism

Apart from the general slowing of metabolism characteristic of the hypothermic state there are changes which should be remembered by those who are employing this slowing to facilitate surgery in patients Wynn (1954) has drawn attention to the hyperglycaemia which occurs during hypothermia in patients During the cold state glucose is metabolized slowly, and if glucose is given during the procedure as in a dextrose infusion a marked hyperglycaemia may develop This may result he suggests, in dilution of the extracellular fluid with intracellular water and the plasma sodium and protein levels will fall He suggests that infusion should be of 2 5 per cent dextrose instead of the usual 5 per cent strength

The effect of cold on the endocrine function is still little understood The administration of thyroxine for 13 days previous to cooling hastened the cooling process in dogs (Hegnauer and Penrod, 1950)

Much has been written about the severe stress reaction which follows exposure of warm blooded animals to cold, and fears expressed that this might result in exhaustion and be a danger in the clinical use of hypothermia It has been suggested that the surface method of cooling might be particularly hazardous in this respect (Delorme, 1952) To this stress Knocker (1955) attributed the severe changes she found in the liver, kidneys and suprarenals Definitive work remains to be done to determine the effect of acute cooling in the absence of shivering and vasoconstriction on the human body s recuperative reserves Certainly the very considerable clinical experience gained does not suggest that any stress reaction that may occur in patients cooled by the methods in current use is sufficient to detract from the advantages of the procedure when it is indicated

It has been suggested that at low temperatures the animal body loses the usual pituitary adrenal response to trauma such as surgery (Khalil 1954) It is conceivable that the absence of this response during the actual surgical procedure might preserve intact pituitary adrenal reserves for the recovery period and thus be beneficial On the other hand further work would seem to suggest considerable

over activity of this response during recovery from hypothermia (Gray and MacPhee, 1958)

INDICATIONS FOR HYPOTHERMIA

There are both surgical and therapeutic indications for the use of hypothermia but as has been seen the principle underlying both is to reduce temporarily the oxygen requirements of the vital tissues, especially those of the central nervous system

There are many reports of the use of hypothermia to permit suspension of the circulation during operations on the heart (*see* for example, Lewis and Taufic, 1953, Virtue 1955, Brock, 1956 Sellick, 1957) There are two limiting factors to this application of the technique The time for which circulatory arrest may be permitted is still severely limited The maximum permissible period at a tempera ture of 28° C is probably around six with an absolute maximum of ten minutes and lowering the temperature a further 3° C increases the hazards without greatly increasing this time Secondly this work is bedevilled by the ever present danger of ventricular fibrillation which, as has been seen may be precipitated by the cardiac manipulations the alterations in circulatory dynamics which must follow on such operations, and by the metabolic acidosis which is a sequel of circulatory occlusion Considerable protection is afforded by the manoeuvres which have been reviewed, especially by the establishment of a respiratory alkalosis by hyperventilation and possibly by the control of serum potassium but the hazard is always present Although ventricular fibrillation may be reversed by electrical shock an effective heart action is much less likely to be re established if there is myocardial abnormality such as hypertrophy or in older patients The consensus of opinion, at present is that the degrees of hypothermia which are safely attain able are useful only for operations such as open atrial septal defect repairs and for pulmonary stenosis in young subjects Older subjects or those in whom there is an established degree of pulmonary hypertension do not do well under hypothermia Ventricular septal defect repairs must be tackled with some form of heart lung pump to permit cardiac bypass It is possible that the differential brain cooling described by the Japanese workers may extend the period available for intra cardiac manipulation up to about 25–30 minutes but this approach has not yet been fully explored

Surgery on the great vessels occasionally may demand hypothermia In coarctation of the aorta the collateral circulation is usually adequate to permit prolonged aortic occlusion during the insertion of grafts, but hypothermia has been found useful by DeBakey and Cooley (1954) Although hypothermia has been used by Bigelow and Greenwood (1954) for mitral surgery there is a consider able risk of irreversible ventricular fibrillation occurring when there is a diseased myocardium (Dundee, Scott and Mesham 1953 Bailey and his colleagues 1954)

It is in neurosurgery that hypothermia is likely to find its most consistent application Burrows and his co workers (1956) have described the technique Under hypothermia not only are very prolonged periods of extreme hypotension tolerated, but clamping of major cerebral vessels during treatment of cerebral aneurysms and vascular tumours is practicable The decrease in cerebral blood flow, brain volume, intracranial pressure and venous pressure are all very advantageous in this type of surgery (Rosomoff 1956)

Procedures other than neurosurgery occasionally demand prolonged hypotension in patients who would not under normothermic conditions be considered suitable for a lowering of blood pressure, and hypothermia is extremely helpful in such cases (Gray, 1955)

Moderate cooling has been employed in the treatment of diseased conditions characterized either by hypermetabolism or by some interference with cerebral circulation Two cases of severe thyrotoxic crisis are reported by Dundee, Grey Mesham and Scott (1953) to have been treated successfully by hypothermia, and encouraging results have been obtained in patients who have hypermetabolism due to hyperthermia as occurs in some cases of poliomyelitis (Miorner, Haeger and Ryd 1955)

Two types of neurological disorder may call for this treatment There are reports of its use in intracranial ischaemic lesions and pyrexias of hypothalamic origin (Sedzmir, Jacobs and Dundee, 1955) when there has been a disturbance of the heat regulating mechanism It is also indicated when cerebral oedema is exacerbating an ischaemic or anoxic cerebral lesion, as after cardiac arrest during operation It cannot be sufficiently stressed that such conditions will respond only if treatment is prompt before serious damage has occurred It is this time factor which will limit the application of hypothermia in cases of coal gas poisoning

CONCLUSION

Hypothermia is a practical procedure and is safe when the temperature is lowered only to 29 -30° C and particularly so where there is no direct tactile stimulation of the heart Its future is established in neurosurgery and other fields as an adjuvant to hypotension It has not yet been fully exploited in cardiac surgery, chiefly because of the high incidence of ventricular fibrillation and the danger of using those lower temperatures which would permit prolonged circulatory arrest There is undoubtedly a trend towards the use of some form of heart-lung apparatus in this field, but further research may yet prove that hypothermia either combined with such apparatus or used alone has advantages The field of deep hypothermia which has been explored in animals opens up prospects for human application which would extend enormously the scope of radical surgery both cardiac and general This may yet prove practicable and the imagination may take flight and envisage the implications of such an approach not only in surgery of election, but particularly in the treatment of large scale casualties during both war and peace

REFERENCES

Adolph E F (1951) *Amer J Physiol* 166 755

Andjus R K (1951) *C R Acad Sci (Paris)* 232 1591

— and Lovelock J E (1955) *J Physiol* 128 541

— and Smith A V (1955) *Ibid* 155 355

— Knopfelmacher F Russell R W and Smith A V (1955) *Nature* 176 1015

Bailey C P Cookson B A Downing D F and Neptune W B (1954) *J thorac Surg* 27 73

Bering E A Jr Taren J A McMurray J D and Bernhard W F (1956) *Surg Gynec Obstet* 102 134

Bernard C (1876) *Lecons sur le Chaleur Animale* Paris Baillère

Bigelow W G and Greenwood W F (1954) *Surg Clin N Amer* 875

— Hopps J A and Callaghan J C (1952) *Can J med Sci* 30 185

— Lindsay W K Harrison R C Gordon R A and Greenwood W F (1950) *Amer J Physiol* 160 125

Blades B and Pierpoint C (1954) *Ann Surg* 140 557
Boerema J Wildsent A Schmidt W J H and Brockhuysen L (1951) *Arch Chir Neerl* 3 25
— Kroll J A Meyne N G Lokin, E Kroon B and Huiskes J W (1956) *Arch Chir Neerl*, 8 197
Brewin E G Gould R P Nashat F S and Neil E (1955) *Guy s Hosp Rep* 104 177
Brock R C (1956) *Proc R Soc Med* 49 347
Brom A G (1957) Personal communication
Brooks C McC Hoffmann B F Suckling E E and Orias O (1955) *Excitability of the Heart* New York and London Grune and Stratton
Burrows M M Dundee J W Francis I Ll Lipton S and Sedzmir C B (1956) *Anaesthesia* 11 4
Burton A C and Edholm O G (1955) *Man in a Cold Environment* London Arnold
Cookson B A and Di Palma J R (1955) *Amer J Physiol* 182 447
— Neptune W B and Bailey C P (1952) *J int Coll Surg* 18 685
Covino B G and Williams L (1955) *Amer J Physiol* 181 362
— and Hegnauer A H (1955) *Ibid* 181 553
— — (1956) *Surgery* 40 475
Davis T R and Mayer J (1955) *Amer J Physiol* 181 669
DeBakey M E and Cooley D A (1954) *J Amer med Ass* 155 1398
Delorme E J (1952) *Lancet* 2 914
Dill D B and Forbes W H (1941) *Amer J Physiol* 132 685
Dundee J W Scott W E B and Mesham P R (1953) *Brit med J* 2 1244
— Gray T C Mesham P R and Scott W E B (1953) *Brit med J* 2 1237
Edwards W S Tulley S Reber W E Siegel A and Bing R G (1954) *Ann Surg* 139 275
Fisher B Russ C Fedor E Wilde R Engstrom P Happel J and Prendergast P (1957) *Arch Surg Chicago* 71 431
Fleming R (1954) *Arch Surg Chicago* 68 145
Gollan F Tysinger D S Jr Grace G Y Kory R C and Meneely J R (1955) *Amer J Physiol* 181 297
Gray T Cecil (1955) *Proc R Soc Med* 48 1083
— (1957) *Lancet* 1 383
— and MacPhee I W (1958) *In Press*
Hegnauer A H and Penrod K E (1950) *A F Tech Rep* 5912 Feb
— and Covino B G (1956) *Amer J Physiol* 186 511
Helmsworth J A and Cole W R (1956) *Arch Surg Chicago* 73 481
— and Covino B G (1957) *Amer J Physiol* 186 511
— Stiles W G and Elston W (1955) *Surgery* 38 843
Horvath S M Rubin A and Faltz E L (1950) *Amer J Physiol* 181 376
Khalil H H (1954) *Brit med J* 2 733
— and MacKeith R C (1954) *Ibid* 4 734
Kimoto S Sugie S and Asano K (1956) *Surgery* 39 592
Knocker P (1955) *Lancet* 2 837
Krogh A (1916) Quoted by Martin C J (1930) *Lancet* 2 561
Lewis T (1930) *Heart* 15 177
Lewis L J and Taufic M (1953) *Surgery* 33 52
Lougheed W M Sweet W H White J C and Brewster W R (1955) *J Neurosurg* 12 240
Lucas B G B (1956) *Proc R Soc Med* 49 345
Lynn R B Melrose D G Churchill Davison H C Cookson B and McMillan I K R (1954) *Ann R Coll Surg Engl* 14 267
Mayer J H Heider C Morris G C Jr and Handley C (1957) *Ann Surg* 146 152
McMurrey I D Bernhard W F Taren J A and Bering E A Jr (1956) *Surg Gynec Obstet* 102 75
McQuiston W O (1950) *Arch Surg Chicago* 61 892
Melrose D G (1954) Cited by Scurr (1955)
Miorner G Haeger K and Ryd H (1955) *Lancet* 2 593
Montgomery A V Prevedel A E and Swan H (1954) *Circulation* 10 721
Niazi S A and Lewis F J (1955) *Surg Forum* 106 Philadelphia Saunders
Osborne J J (1953) *Amer J Physiol* 175 389

Parkins W M Jensen J M and Vars H M (1954) *Ann Surg* 140 284
Penrod K E (1951) *Amer J Physiol* 164 79
Prevedel A E Montgomery V and Swan H (1954) *Proc Soc exp Biol N Y* 85 596
Radigan L R Lombardo T A and Morrow A G (1956) *Surgery* 40 471
Riberi A Siderys H and Shumacker H B (1956) *Ann Surg* 143 216
Rosomoff H L (1956) *Proc R Soc Med* 49 358
Ross D N (1954) *Lancet* 1 1108
— (1957) *Proc R Soc Med* 50 76
Scurr C F (1955) *Proc R Soc Med* 48 1077
Sealy W C Young W G Jr and Harris J S (1954) *J thorac Surg* 28 447
Sedzmir C B Jacobs D and Dundee J W (1955) *Brit J Anaesth* 27 93
Sellick B A (1957) *Lancet* 1 443
Selye H (1946) *J clin Endocrin* 6 117
Smith A V (1956) *Proc R Soc Med* 49 357
Spurr G B Hutt B K and Horvath S M (1954) *Amer J Physiol* 179 139
Swan H (1954) *J thorac Surg* 28 478
— and Zeavin I (1954) *Ann Surg* 139 385
— — Blount S G and Virtue R W (1953a) *J Amer med Ass* 138 1081
— Zeavin I Holmes J H and Montgomery J (1953b) *Ann Surg* 138 360
Virtue R W (1955) *Hypothermic Anesthesia* Illinois Thomas
Wynn V (1954) *Lancet* 2 575
Zeavin I Virtue R W and Swan H (1954) *Anesthesiology* 15 113

CHAPTER 10

CARDIO-RESPIRATORY PUMPS

D G MELROSE

THE CORRECTION of an intracardiac abnormality demands access to the interior of a bloodless and motionless heart An unhurried and effective repair can be achieved in all but the simplest lesion only if a method is available for protecting the vital centres from the consequences of circulatory arrest for periods in excess of thirty minutes No modification of the principle of hypothermia can at present allow of such operating times, and it is generally accepted that the function of the heart and lungs should be maintained during prolonged procedures by a heart-lung machine These machines are in use in several centres throughout the world, and while by no means perfect have established a new approach to the treatment of cardiac disorders

THE OXYGENATOR

Imitation of the function of the lungs remains the most difficult problem, and it is here that opinion is most sharply divided In all, four different approaches are being explored three of which are wholly artificial, and one involves substituting for the normal lung a lung taken from another animal

Homologous animal lung

The homologous animal lung is a very efficient mechanism for the oxygenation of blood and represents a near physiological method It is, however, not readily prepared and does not lend itself to the maintenance of good sterile technique An alternative to the isolated homologous lung has been suggested whereby a portion of the animal s own lung is used but cannulation of the pulmonary veins is exceedingly difficult and little success yet attends this attractive possibility

Artificial systems

Semi permeable membranes

Of the wholly artificial systems the one which most nearly approaches physio logical conditions is that involving the use of semi permeable membranes This technique has evolved from experiences with the artificial kidney However the membranes available scarcely allow an adequate gas exchange and their use is limited Those which have been found most useful at the time of writing are made of ethyl cellulose or polyethylene The most efficient transmission of oxygen through such membranes to date was obtained with an ethyl cellulose film

one thousandth of an inch thick which allowed the diffusion of 14 6 cubic centimetres of oxygen per square metre per minute When using a film so thin, considerable mechanical problems have to be overcome in the design of an oxygenator based on this principle However this technique deserves further investigation (Clowes, Hopkins and Neville, 1956, Kolff and his colleagues, 1956) Work proceeds on the use of Teflon film which possesses a greater diffusion constant than ethyl cellulose and also is mechanically more durable Should this material fulfill its promise it may well be that a disposable unit could be made capable of exchanging sufficient gas to provide for the needs of adult man

Direct exposure of blood to oxygen

The two methods most commonly chosen are those which involve exposure of blood directly to oxygen In one method blood is filmed on bubbles of oxygen In some designs these bubbles are microscopic and dense foam is created (Clark, Gollan and Gupta 1950) In others the bubbles are larger, the foam produced is much less dense, and less difficulty attends the reconstruction of blood free from gas bubbles (Clowes, 1954)

A large variety of designs to accomplish this form of oxygenation have been described, one of which, the oxygenator ascribed to DeWall and his colleagues (1956) is used extensively in clinical practice (Fig 19) In it large bubbles are formed as oxygen is dispersed in blood and these pass up a vertical tube of polyvinyl chloride At the top of this tube is a de bubbling chamber containing a silicone anti foam compound from which the defoamed blood is allowed to descend in a spiral of wide bore tubing This helix acts as a settling chamber and also as a reservoir from which oxygenated blood can be pumped The tubing is disposable and the unit is newly constructed for each perfusion

A more recent modification of this, also disposable is a single polyvinyl chloride unit in the form of a plastic bag (Hyman 1956) The simplest description of this is that of a pair of plastic trousers up one leg of which the bubbles climb and, after defoaming at the top, cascade down the other leg as blood It is likely that a great variety of fully disposable units will eventually be produced for this is undoubtedly the simplest method of oxygenating blood However, it is not yet known what physicochemical alterations to the blood such bubbling devices cause nor whether any such changes are in fact important

The bubble oxygenator has allowed several hundred intracardiac operations to be performed with a mortality of between 20 and 25 per cent However, it has been repeatedly demonstrated in surgery that a new technique, even in the hands of the finest exponents, carries an alarming mortality but if this is placed against the inevitable early death of a large proportion of these patients it represents a very significant advance This device has not solved the many problems of cardiac surgery, and it cannot be denied that the system has certain limitations and is best used in circumstances in which perfusion rates are low and operation times are short Improvements may fully overcome the present disadvantages and give to this relatively simple device a much wider application

The bubble oxygenator has in the main been used in association with what is known as the low flow principle This principle was derived from the experiments of Andreasen and Watson (1953) who showed that provided the azygos vein was unobstructed occlusion of both the superior vena cava and the inferior vena

cava could be maintained for periods of up to thirty minutes without the subsequent death of an animal The blood flow carried by the azygos vein allowed a cardiac output of only about 10 per cent of the normal, but this low flow was in fact sufficient These experiments led Cohen and Lillehei (1954) in their human perfusions to use perfusion rates of between 20 and 30 per cent of the expected cardiac output

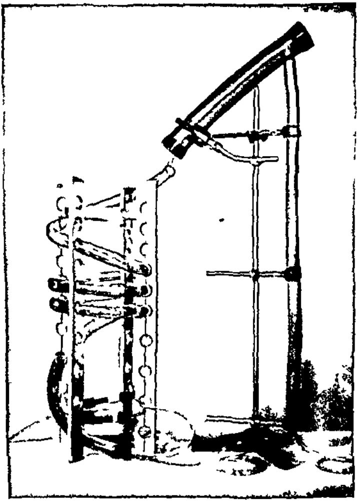

FIG 19 —The bubble oxygenator of DeWall and Lillehei The vertical tube forms the oxygenating chamber from which foam emerges to descend through the spiral tubing being debubbled as it flows

This low flow in combination with the bubble oxygenator has undoubtedly proved effective though certain penalties are attached to it A severe metabolic acidosis is created by this inadequate perfusion and it is probable that full replacement and more exact imitation of normal circumstances should be attempted The primary object of the cardiac bypass procedure is to allow surgeons adequate time to repair defects within the heart and if it is a feature of the low flow principle that this time is limited because of alterations to the acid base balance it must surely prove but a stop gap procedure

That the guiding principle should be the full replacement of the circulation with adequate reserves of oxygenation and flow rate is the firm conviction of the group of surgeons physiologists anaesthetists and others at the Mayo Clinic (Kirklin and his colleagues 1955) This team has demonstrated a remarkable mastery of all the problems involved They have chosen a method of oxygenation which involves the direct exposure of blood to gas but which does not involve the bubbling of gas through blood This principle whereby blood is spread in very thin films and exposed directly is one of the oldest known To enumerate the many methods described to ensure the provision of large surface areas would involve a lengthy historical review Three examples will make clear the principles Von Frey and Gruber (1885) in their artificial lung allowed blood to spread in a thin film over the inner surface of a cylinder which was filled with oxygen The surface area was approximately half a square metre Variants of this were tried in succeeding years but proved ineffective Bjork (1948) in Stockholm described a machine using rotating discs to expose films of blood to oxygen In this machine forty or fifty discs dip into a trough of blood When rotated they pick up on their surfaces thin films of blood and in this way create a large gas-liquid interface the surface area exposed being continually renewed as the discs rotate This device was a great deal more efficient than any previously described and did much to renew interest in this type of oxygenator

Vertical screen principle

Miller Gibbon and Gibbon (1951) described an oxygenator in which the blood was streamed over a number of wire gauze screens These screens are stationary and as blood descends over them the turbulence of their passage exposes a great number of cells to oxygen In order to make more efficient such a system which has of itself no moving parts the blood is recirculated within its own pulmonary circuit

It is this method of oxygenation which has been so brilliantly utilized by the workers at the Mayo Clinic Using Gibbon s machine as a model, they have constructed an artificial heart and lung capable of circulating and adequately oxygenating over 5 litres of blood per minute without serious destruction of its elements (Fig 20)

Two disadvantages attend the use of the vertical screen principle One is the difficulty involved in creating a uniform film of blood over the screens for there is a tendency for rivulets to form which immediately limit the area of blood exposed The screens themselves cannot be allowed to dry while *filming is in* progress, and hence the film once established cannot be broken without danger of failure to reconstitute it Thus the oxygenator once charged must be kept running throughout what may be a long waiting period

The second difficulty is occasioned by the fact that the faster the blood flows over the screens the more blood is in fact held on the screens themselves Therefore the blood volume of the artificial lung tends to increase with the flow rate and in order to control this a flow rate through the pulmonary circuit in excess of any expected during perfusion must be established and *maintained* These disadvantages are only practical ones and should be eradicated in the future New materials may themselves bring relief from these problems and eliminate the present disadvantages

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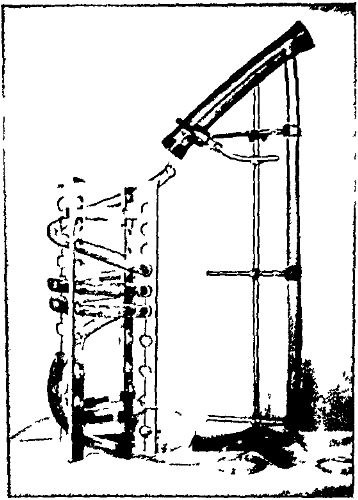

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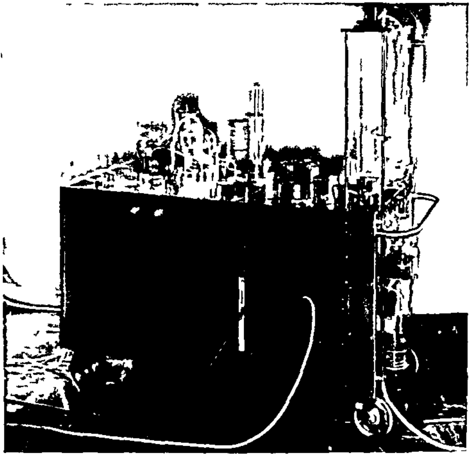

FIG 20 —A vertical screen oxygenator is a prominent feature at the right hand end of the machine in use at the Mayo Clinic

Rotating disc oxygenator

When this problem was taken up at the Postgraduate Medical School of London in 1949 it was decided that the rotating disc oxygenator should be used Simple enlargement was rejected and a novel design adopted In this machine blood passes along a rotating cylinder set at 20 degrees to the horizontal (*see* Fig 21) In the cylinder thin plastic discs are so arranged that they form crescentic protrusions into the lumen of the cylinder As the cylinder rotates these discs pass under the blood and then up into the gas mixture where the adherent blood films are oxygenated When rotating at 100 revolutions a minute the available surface area exposed is in the region of 120 square metres and oxygen can be introduced into the blood at rates of more than 100 millilitres per litre per minute Destruction of the cellular elements of blood is slight and but little deposition of fibrin occurs

Conclusions

As yet no full comparison of the methods discussed has been possible It is only now that technical progress in the application of these machines has reached a sufficient degree of consistency to warrant such a comparison It is likely that in the near future a re assessment of the position will be undertaken Not only must the actual efficiency and effectiveness of each of these methods be taken into

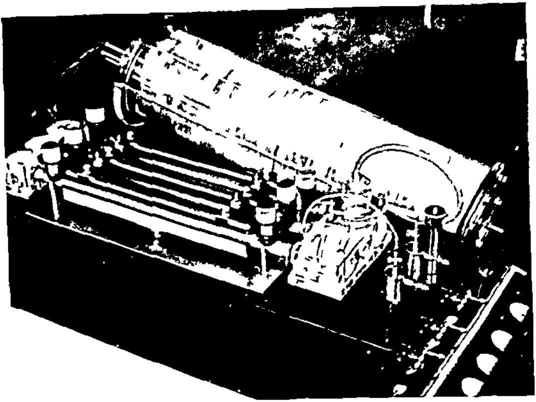

FIG 21.—The rotating disc oxygenator is seen in this figure behind the pumping unit

account, but a study of their practicability will often reject an excellent solution on grounds of complexity, of expense, or of difficulty in maintenance or cleaning Although fully disposable systems have the most appeal, they may also be prohibitively expensive It is sometimes better to clean thoroughly a well made item than to risk possible defects in manufacture in a replaceable one

THE PUMPING CIRCUIT

If the number of varieties of oxygenators is large it is greatly exceeded by that of the pumps offered However these pumps can be divided into two main types On the one hand there are those pumps whose action is intermittently to empty the pumping chamber the direction of flow being controlled by valves, and on the other hand there are those in which an elastic tube through which the blood passes is squeezed within the pump either by the action of a roller or by the compression of fingers, the rollers or fingers acting both as the pump and as the valves The essential difference between these two types is that in the first instance control of the output of the pump may be both by changing the rate of the pump stroke and also by altering the length of the stroke, whereas in the second type only a change in rate at which the pump works is possible The pump described by Dale and Schuster (1928) is a good model of the first type, while the roller pump of Jouvelet (1934) or that of DeBakey (1934) typifies the second group The finger pump is essentially a roller pump and should be regarded as such

In use the difference between these two types becomes obvious The intermittent

pumps employing valves to control the direction of flow can be made to imitate closely the normal shape of the pulse, while the roller type of pump tends to have a continuous output and a minimum pulse component

The most widely used pump today is that manufactured as the Sigma motor pump which uses compressing fingers (Fig 22) Just as the bubble oxygenator is particularly suitable for the low flow type of perfusion, so is this form of pump most effective at low flows It is convenient, inexpensive but limited in output Attempts to obtain high flows result in considerable destruction of cells

The Gibbon apparatus at the Mayo Clinic uses the roller pump of DeBakey and no difficulty is found in pumping at flow rates in excess of 5 litres per minute Both these pumps produce an almost continuous flow with minimum pulse and

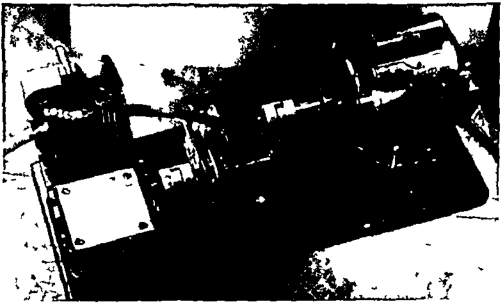

FIG 22 —The Sigma pump

although no definite evidence exists as to whether a pulsatile flow is necessary it may be important, and a pump has been designed which seems closer to the ideal (Fig 21) (Melrose, 1955)

In it a simple straight rubber or plastic tube is squeezed by compression plates one plate acting as a back stop against which the other plate presses the tube The pumping plate is driven by a cam shaft which imparts an undulating movement to it The back stop can be moved towards or away from this moving plate and hence the amount of compression can be varied and with it the stroke volume In practice a variation of output between 0 and 5 litres per minute can be obtained in this manner Such a pump of course requires valves to direct the flow and in order to maintain the advantages of the roller pump in this respect these valves do not lie within the blood stream They are essentially miniature versions of the pumping plates and completely occlude the tubing at appropriate points in the pumping cycle which provides a close imitation of the normal ventricular cycle In this design the tubing is only compressed completely at the valve sites and hence there is little danger of blood destruction by the apposition of the walls of the tube in the pump chamber It is this apposition of the tube walls throughout its whole length in the roller type of pump which endangers the blood cells

It will be seen that no hard and fast rules yet exist to govern the design of pumps. Again the considerations of practical utility have to be balanced against the claims of physiological imitation. It is clear, however, that the pump must be capable of maintaining a blood flow through it of at least 4 litres a minute against normal vascular resistance, that as smooth a flow as is possible through the pump should be established, that the material with which blood comes in contact should be inert and non-toxic, that the pump chamber should be capable of sterilization and that complete mechanical reliability must be expected. Simplicity, ease of maintenance, and accuracy of control of the output from the pump are also valuable attributes.

THE BYPASS PROCEDURE

The mechanical aspects of the heart-lung machine are only a small part of the technique of the bypass procedure, which must become the responsibility of a team experienced not only in the surgery of the heart but skilled in the measurements of vascular pressures, and of biochemical and haematological changes.

Certain broad principles are agreed at this time to govern the technique of connecting heart-lung machines to the patient or animal, to prevent blood coagulation and its attendant problem of re-establishing a normal clotting time after perfusion, and to avoid severe metabolic alterations.

Cannulation

It is generally agreed that venous blood should be extracted from the great veins entering the heart by wide bore tubes, and in practice it is usual for these

FIG. 23.—A stainless steel cannula such as is inserted into the subclavian artery
(By courtesy of the Genito-Urinary Manufacturing Co Ltd)

tubes to be passed into the superior and inferior venae cavae through the right atrial appendage. This is particularly necessary when blood is allowed to flow freely from these veins without the assistance of a suction pump. As yet there is no complete agreement on the vexed problem of how to ensure the maximum flow from the veins: some rely on gravity, others on direct suction, but all are agreed that as large a calibre tube as possible should be inserted close to the entrance of the great veins into the heart.

For the return of oxygenated blood into the arterial side the most usual site is the left or right subclavian artery. The subclavian artery is of large bore, is close to the vital centres and can be sacrificed if need be without danger. Into this vessel can be inserted a cannula capable of carrying the normal cardiac output for that particular patient without the imposition of a high resistance to the inflow of blood. It is essential that a variety of cannulae (Fig. 23) are at hand to ensure that the largest that will fit into any given subclavian artery can be

inserted The interference to blood flow created by a very narrow cannula creates considerable destruction of red cells and seriously hinders perfusion An alternative to the subclavian is the femoral artery, which is always repaired at the conclusion of the bypass

Pressure measurement

The measurement of the arterial pressure and also that within either the superior or inferior vena cava by direct cannulation should be regarded as essential That obtaining in the great veins is a most important factor in establishing a successful perfusion The rate at which the perfusion can be performed must depend wholly on the rate at which blood can be obtained from the venous system Additional suction from the veins can have no effect other than to collapse them and to bring the perfusion to a halt It is thus essential to maintain a perfusion rate which keeps the central venous pressure as normal as possible, and it is most useful to have a continuous measurement of this value both before, during, and after perfusion A rise in venous pressure indicates that the perfusion rate is not being maintained at the highest possible level Here, of course, the subject gets more controversial, for in the low flow system a high venous pressure is expected because the perfusion rate is arbitrarily about one third of the normal cardiac output

A record of the arterial pressure when taken in conjunction with that of the central venous pressure gives a reliable index of the state of the heart, and the onset of heart failure can be readily appreciated The arterial pressure is used also to detect changes in the size of the vascular bed and to reflect the vasomotor tone

Electrocardiography and electroencephalography

Two other quantities which should if possible be measured continuously are those provided by the electrocardiogram and the electroencephalogram Though little change is normally found in the electrocardiogram alteration of the T wave is a sensitive index to chemical change in the blood, and of course the onset of arrhythmias gives warning of the possibility of ventricular fibrillation The recording of the electro cardiogram may well be continued for many hours post operatively because the extensive repair of some cardiac defects gives rise to considerable anxiety during the period of operative recovery

Detailed interpretation of the electroencephalogram is not a necessity, but alteration of the normal *alpha* and *theta* rhythms particularly towards the slow *delta* rhythm signify a failure to perfuse sufficiently and oxygenate the brain As patients are normally only lightly anaesthetized during cardiac surgery the effect of anaesthetic agents is minimal and alterations to the electroencephalographic pattern are of serious import It has been the experience of many that even an apparently satisfactory bypass procedure may come to naught due to undetected cortical damage if this measurement is neglected

Elective cardiac arrest

Simple bypass of the heart and lungs does not cause the heart beat to cease and it is essential to nourish the active myocardium by maintaining an adequate coronary blood flow This blood flow may be substantial, and draining as it does into the right atrium and right ventricle it may greatly hamper the visualization and repair of intracardiac defects An additional problem is posed by the possibility of the beating heart ejecting air into the great vessels from its open

cavities To overcome these hindrances the heart beat must be arrested in such a way that it will restart at will and the coronary circulation must be halted during the period of the intracardiac manipulations

Reference to the discovery of Ringer (1883) of the effect of different cations on the heart beat provides a technique for achieving this The injection into the coronary circulation of potassium citrate so that a concentration greater than one milligram per millilitre is created in these vessels will arrest the heart beat in diastole and will maintain the quiet state so long as the concentration persists (Baker and his colleagues 1957) Normal beating is restored when simple perfusion of the coronary arteries washes out the potassium citrate solution

The oxygen consumption of the quiescent heart is low, and even at normal body temperature a period of myocardial ischaemia of 15 to 20 minutes does not endanger such a heart

This manoeuvre has ample experimental and clinical background and should be regarded as a necessary adjunct to the bypass procedure offering as it does an opportunity for surgery within the motionless, flaccid heart and without the danger of air embolism

Blood volume

Very considerable care must be exercised in regard to the blood volume Accurate estimations of blood loss must be made throughout the procedure and full replacements immediately made Care must be taken to avoid the consequences of the injection of large quantities of fluid which though isotonic may in fact not be isosmotic A higher proportion of failure particularly in those cases already incapacitated by pulmonary damage is likely if severe haemodilution occurs So seriously do the workers at the Mayo Clinic consider this problem that they take special care by adding human albumin to preserve the isosmotic value of any fluid used either to maintain an intravenous route or to flush through cannulae or catheters used for measurement The smaller the patient the more important this aspect is and the more essential it is to preserve a normal blood volume Weighing before and after perfusion should be carried out and readjustments made to ensure no overloading of the vascular system

Anticoagulants

All machines require a certain amount of blood to charge them This blood must be fresh blood taken through non wettable tubing into non wettable containers The anticoagulant used should in general be heparin and a generally agreed concentration for this is 15 milligrams of heparin to each 500 millilitres of blood stored Coagulation is prevented in the patient or animal by the intravenous injection of heparin Alternatives exist but heparin is the most common substance used Though in some respects inadequate particularly in regard to the change in the actual physical properties of blood which heparin creates heparin has the merit of being a naturally occurring substance whose action can be reversed The reversal can be brought about by the injection of protamine sulphate which forms a loose bond with free heparin in the blood and neutralizes its anticoagulant effect

Protamine is not without dangers and of itself creates clotting problems if given in excess It has an additional disadvantage of affecting the blood pressure

if given rapidly or in too high a concentration A workable rule is to obtain a heparin level in excess of 2 milligrams per kilogram of body weight in the blood and to reverse this at the end of perfusion with an equal quantity of protamine after which a clotting time examination is made If this value is less than twice normal no further protamine need be given If it is greater than this then a protamine titration test should be done (Perkins and his colleagues 1956) and additional protamine given During the three hours succeeding perfusion it is useful to infuse slowly a quantity of protamine equal in amount to that given to neutralize the heparin

Failure to re establish a normal coagulation time following a bypass procedure may be due to many complicated effects There can be no doubt that platelets are usually deposited on the artificial material of which the apparatus is constructed and it is known that a form of defibrination of the blood frequently takes place This is not obvious and does not often lead to frank clotting However it does lead to the consumption of many clotting factors, and the only way in which this can be prevented is to ensure that the heparin level is not allowed to fall unduly during perfusion The treatment of the bleeding tendency sometimes found is at present confined to replacement of blood, and in some instances to the addition of fibrinogen Blood must be quite fresh and must be drawn with the same precautions as those used to charge the machine, namely through non wetting surfaces into non wetting containers A direct transfusion can be of enormous value in cases of severe bleeding tendency A point to note in this context is that if the blood is allowed to cool during passage through the machine the tendency to bleed will be exaggerated This problem merits further study for it is by no means solved and continues to jeopardize the bypass technique

Materials

The effect of passing blood over foreign surfaces is variable, and many of the difficulties associated with coagulation deformities following perfusion are in fact due to the use of inappropriate materials

The advent of new plastic materials whose surface can be rendered quite non wettable and whose composition is non toxic has greatly simplified the choice Platelets leuco cytes and inevitably fibrin will adhere to rough surfaces to those contaminated by debris and particularly to those exerting strong chemical attraction In this respect untreated glassware is suspect as is rubber in which there is an excess of chemical fillers Pure latex and glass whose surface has been rendered inactive by a coating of silicone is less guilty in this respect Probably the finest material from which to make apparatus at present is polytetrafluorethylene This has as its trade names Fluon and Teflon Unfortunately it is very expensive and most workers are content with either Perspex or polyvinyl chloride These two though in most respects ideal cannot be safely autoclaved and while chemical sterilization is undoubtedly effective there are many who would prefer to add to such a method the more traditional one of autoclaving

Whatever the material the surface to which blood is to be exposed must be as smooth as possible It has been found that stainless steel is an excellent material provided it is given the finest polish and is particularly suitable where rigid parts are required The choice of materials grows ever larger and it is safe to say that the precise require ments will in future be met

The use of silicone compounds has been particularly rewarding Not only will

certain of these make inert otherwise active surfaces but others of the same group have the remarkable ability to defoam blood without in any way injuring the blood itself The resurgence of interest in the bubble type of oxygenator is wholly dependent upon the discovery of Silicone antifoam A

Filtration

The necessity to filter all the blood coming from the machine has not been established However, normally the lungs shield the cerebral and coronary vessels and probably filter out aggregations of protein and other cellular debris This can be imitated by screens of fine mesh but if these screens are to be fully effective against such particles they constitute a gross impediment to flow, and may of themselves contribute largely to the destruction along the tubes Most workers are content to screen only those particles which will not pass through relatively large meshes and it is usual to employ a mesh of between 100 and 250 In order that hold up by such a filter should not be excessive large areas of mesh must be used Frequently the filter can be combined with an air trap in the circuit

CONCLUSIONS

These then are some of the associated problems with their present solutions There are many more, particularly those concerned with the physiological response to the bypass procedure Little is known of the physiological mechanism brought into play when the heart and lungs are bypassed The behaviour of individual organs is unstudied, and even the effect on the cellular elements of the blood itself awaits more refined techniques of determining cell survival and function However, a point in development has undoubtedly been reached from which it is possible to look forward to an increasing concentration on such problems rather than those of mere survival

REFERENCES

Andreasen A T and Watson, F (1953) *Brit J Surg* 40 616

Baker J B E Bentall H H Dreyer B and Melrose D G (1957) *Lancet* 2 555

Bjork V O (1948) *Acta chir scand Supp* 137 96

Clark L C Jr Gollan F and Gupta V B (1950) *Science* 3 85

Clowes G H A Jr Neville W E Hopkins A Anzola J and Simeone F A (1954) *Surgery* 36 557

— Hopkins A and Neville W E (1956) *J thorac Surg* 32 630

Cohen M and Lillehei C W (1954) *Surg Gynec Obstet* 98 225

Dale H H and Schuster E H J (1928) *J Physiol* 64 356

DeBakey M E (1934) *Med surg J* 87 366

DeWall R A Warden H E Read R C Gott V L Ziegler N R Varco R L and Lillehei C W (1956) *Surg Clin N Amer* 36 1025

Frey M von and Gruber M (1885) *Arch Anat Physiol, Lpz* 9 519

Hyman E S (1956) *Trans Amer Soc art int Organs* 2 1

Jouvelet P (1934) *Bull Soc Méd Hop Paris* 50 537

Kirklin J W Dushane J W Patrick R T Donald D E Hetzel P S Harshbarger H G and Wood E C (1955) *Proc Mayo Clin* 30 201

Kolff W J Effler D B Groves L K Peereboom G and Moraca P P (1956) *Cleveland Clin Quart* 23 69

Melrose D G (1955) *J Physiol* 127 51

Miller B J Gibbon J H Jr and Gibbon M H (1951) *Ann Surg* 134 694

Perkins H A Osborne J Hurt R and Gerbode F (1956) *J Lab clin Med* 48 223

Ringer S (1883) *J Physiol* 4 29

CHAPTER 11

THE TREND IN OBSTETRIC ANALGESIA AND ANAESTHESIA

HILDA ROBERTS

OBSTETRIC ANALGESIA

THE EVOLUTION of analgesia in labour has produced a multiplicity of drugs and techniques introduced over the past half century The trend has been from neglect to the intense narcotization of twilight sleep , the latter tending to take a toll of infant life This effect made obstetricians more conservative in the use of pain relieving drugs with the result that for a time the average standard of pain relief was poor However in the past two decades various satisfactory techniques have been introduced Although during the antenatal period the care of the patient is hardly within the anaesthetist s realm he should appreciate the value of present day methods of preparation for natural childbirth Some of the claims made by the enthusiasts are extravagant but anything which educates and reassures a woman about labour is valuable

The efficiency of any analgesic drug must be judged according to the following criteria (1) the effect on the mother, concerning pain relief and side effects (2) the effect on the course of labour and (3) the effect on the foetus As yet no analgesic drug has attained the ideal especially with regard to the effect on the foetal respiratory mechanism but the discovery of suitable antidotes has contributed to the safety of morphine and pethidine A review of the analgesic drugs in use indicates that the bromides and chloral hydrate have given way to the more powerful hypnotics and narcotics Nevertheless the former provide an excellent preparation for the subsequent administration of narcotics or inhalational analgesics The hypnotics administered in labour have been mainly barbiturates These drugs which were introduced into obstetrics in 1929 have remained popular although they have little effect on raising the pain threshold if consciousness is maintained The short acting barbiturates are to be preferred and 3 grains of quinalbarbitone given to a restless patient in the early stage of labour followed by more powerful drugs can provide a satisfactory and restful labour Although the barbiturates do not appear to have any direct depressant effect on uterine activity, they can impair the expulsive mechanism of the second stage The degree of depression varies directly with the dosage Instrumental deliveries are more frequent since the patient is disinclined to use her contractions and the resulting inertia may predispose to postpartum haemorrhage Reports vary concerning the effect of these drugs on the newborn but there is reason to believe that there is delay in the onset of breathing and diminished ventilation at birth (Galloway Grier and Blessing 1936)

Pethidine

Pethidine has sedative, analgesic, and antispasmodic properties, and has proved a most valuable drug during labour It has a considerable margin of safety, but shock like reactions have been reported Disturbing as these undoubtedly are their occurrence is infrequent considering the large number of administrations Pethidine can impair the strength of uterine contractions if given ill advisedly Kymograph recordings of uterine activity (Roberts, 1948) indicated that the interval between the contractions can be lengthened by intravenous pethidine or pethidine and scopolamine, but the normal rhythm is resumed after two to three contractions if labour is well established Clinically, the newborn infant seems to be little depressed by average doses but pethidine appears to have the effect of reducing the minute volume for the first few hours of life (Roberts and her colleagues 1957) This respiratory depressant action of pethidine can be offset by the antidotes now available Although levallorphan did not have the effect of raising the mean minute volume when combined with pethidine it did appear to reduce the number of infants born in a state of asphyxia in the series Levallorphan did not impair the analgesic value of pethidine when combined in the ratio of 1 milligram of levallorphan to 100 milligrams of pethidine Nalorphine hydrobromide (Lethidrone), another antidote to the respiratory depression has been reported on favourably

Alphaprodine hydrochloride

Alphaprodine hydrochloride (Nisentil) like pethidine a piperidine derivative, was described as an analgesic by Randell and Lehmann (1948) Personal observations concerning its efficiency showed that, although some patients did not appear to obtain relief they gave a favourable opinion the next day Neither the course of labour nor the foetus suffered any ill effects and the usefulness of the drug lies in its comparatively rapid effect and excretion (Roberts and Wrigley, 1953) Other members of the piperidine ring series have been introduced but none has attained the satisfactory therapeutic level of pethidine The use of amidone (Methadone, Physeptone or Dolophine) has been described by Prescott and Ransome (1947)

Morphine

Morphine and its alkaloids still provide satisfactory results in certain obstetric circumstances but routine use is now rather the exception When other analgesics fail to give relief to a tired patient, morphine will often prove satisfactory According to Wolff Hardy, and Goodell (1940), the efficiency of this drug for pain relief lies in its ability to elevate the pain threshold and replace fear and anxiety by contentment relaxation and apathy inducing lethargy and sleep Reports on the effect of the drug on uterine activity are rather conflicting according to the writings of Bourne and Burn (1930) Dodek (1934) and Embrey (1940)

Diamorphine

Diamorphine (heroin) diacetylmorphine is a drug which proves extremely useful for apprehensive patients but is regarded with a certain amount of disfavour because of its habit forming property Lund and Harris (1943) concluded that diamorphine produced less respiratory depression in the infant than does morphine

Scopolamine

Scopolamine was introduced into obstetrics as the companion drug to morphine, its outstanding ability to produce amnesia made it the operative drug in 'twilight sleep'. There is a narrow margin separating the desirable and undesirable therapeutic effects, but $\frac{1}{150}$ grain added to 100 milligrams of pethidine rarely causes excitement in the normally balanced patient (Roberts, 1948).

Methylpentynol

Bourne (1954) reported that methylpentynol produced satisfactory relief from tension, and promoted analgesia in a fair proportion of women in labour, without interrupting the course of labour or affecting the newborn. Personal observations led to the conclusion that methylpentynol provided a satisfactory state of comfort and relaxation in approximately 40 per cent of women in labour, and that it appeared to enhance the analgesic effect of other drugs.

Tranquillizers

Meprobamate and acetylpromazine are now being introduced, as also is chlorpromazine. Norton and his colleagues (1956) and Schaffer (1956) describe techniques which give satisfactory results. The former combine chlorpromazine with scopolamine and quinalbarbitone, the latter uses only scopolamine as the companion drug. The medication sounds rather elaborate, but the authors of each work record satisfactory analgesia without untoward results. The usefulness of chlorpromazine lies in its tranquillizing property and the potentiation of other drugs used in conjunction with it.

The 'lytic cocktail' of Laborit provides effective relief during labour (Laborit, 1952) and it is possible to administer it by the intravenous route 15–20 minutes before delivery without ill effect to the infant. The potentiation of analgesic drugs by pecazine (Pacatal), a phenothiazine derivative, has been studied by Nieschulz and his colleagues (1954) and clinical observation recorded by Hayward Butt (1957), the latter indicating its usefulness in the obstetric field. He has coined the term 'ataralgesia' to describe the resulting calmness and freedom from pain. A study of 200 patients receiving chlorpromazine, pethidine, and promethazine during labour has been presented by Carroll and Hudson (1955).

Vitamins

Even the vitamins have been employed to ease the discomfort of labour. The writer used vitamin B_1 in 24 patients in labour, as a means of combating physiological pain and accelerating parturition. This has been recommended by Soviet workers. Eighteen patients described a feeling of relaxation and tiredness and 6 of these experienced mild analgesia also. Doses of 80 to 100 milligrams were given intramuscularly at hourly intervals for 3 to 4 doses. The effects of any analgesic drugs given in addition appeared to be potentiated but although labour proceeded satisfactorily in these cases, there did not appear to be any acceleration.

INHALATION ANALGESICS

Nitrous oxide and air

The withdrawal of chloroform capsules for use by the midwives called for some other easily administered method of pain relief. The need was answered by Minnitt

who conducted research into the effectiveness and safety of self administered nitrous oxide in air, and the method and apparatus evolved was accepted by the Central Midwives Board in 1937 for the independent use of midwives The technique is well known and its use has stood the test of time, and the only observation which need be recorded here is a warning on the inevitable reduction of oxygen to the patient using the apparatus It has been shown by Walker and Turnbull (1953) that the oxygen level in the foetal circulation falls to a dangerously low percentage after full term Therefore it can be concluded that the ordinary mixture of gas and air creates an extra hazard for the postmature foetus The intermittent use and quick excretion of nitrous oxide may act as a safeguard during labour There is no doubt that nitrous oxide combined with oxygen instead of air is the most satisfactory inhalation analgesic for labour, but the need for a more intricate apparatus makes it unsuitable for its unsupervised use by the midwife It is a pity that our standard of obstetric analgesia should have to be set by such circumstances

Trichloroethylene

Trichloroethylene has now reached an established position in anaesthesia Jackson (1934) used it as a substitute for the usual narcotics to maintain analgesia over long periods In 1941 Hewer and Hadfield noted the degree of analgesia occurring in the early first stage of anaesthesia, a property which has made it so suitable for obstetric analgesia Various types of inhalers have been designed for the administration of trichloroethylene but since the percentage of vapour varied under certain conditions in the earlier models they were not regarded as suitable for use by midwives The work of Helliwell and Hutton (1949) drew attention to the rapid passage of the drug across the placenta and its consequent accumulation in the foetal tissues After conducting a specially planned trial, a memorandum was published by the Medical Research Council (1954) which recommended that midwives should be allowed to use two approved trichloroethylene inhalers, the Emotril and the Tecota models The final observations of the Special Committee were that (1) trichloroethylene was superior to gas and air in analgesic potency and appeared to be as safe, (2) trichloroethylene may have slight but definite effect on the duration of labour in multiparae and also on the child at birth, but the incidence of dangerous complications in either mother or child was the same as in gas and air (3) the use of pethidine with either trichloroethylene or gas and air results in greater analgesia but tends to prolong labour and increase the frequency of signs of respiratory depression in the child

Isopropyl chloride

Isopropyl chloride was described by MacDonald (1950) in a preliminary report in which he stated that when the drug was used in normal labour the analgesic qualities facilitated the delivery by reason of the patient s co operation and her freedom from pain Similar results were obtained by the writer in a small series of cases The analgesic effect was produced quickly and pleasantly, the patient using the inhaler described by MacDonald The infants were unaffected by the drug, and the third stage was uncomplicated The average length of use by the patients was 4 hours

CONDUCTION ANALGESIA

Although this aspect of obstetrical analgesia has been dealt with in Chapter 6 it would seem appropriate to review briefly current British practice here Kreis introduced conduction analgesia into obstetrics by performing a spinal block for an operative delivery in 1901 Other techniques followed, and in 1909 von Stoeckel injected cocaine into the extradural space *via* the sacral canal At a later date the segmental nerves associated with uterine pain were blocked at the costal margin by Schimpert In 1933 a series of combined paravertebral and low caudal blocks was described by Cleland who also was the first to give details of the accurate nerve supply connected with uterine pain The original technique of epidural analgesia as devised by Dogliotti (1933) has been introduced with success into obstetric practice Reich described yet another conduction method in 1951, that is paravertebral lumbar sympathetic block in labour Since these methods of local analgesia have their application in normal and abnormal labour and delivery they will be considered under these headings

In normal labour and delivery

The most commonly employed method is that of local infiltration This procedure is satisfactory for episiotomy and subsequent repair, and also for the suturing of perineal tears The infiltration is usually made with procaine 0 5 per cent combined with hyalase introducing the fluid fanwise around the area involved If however there is time for an unhurried injection and the foetal head is not too low in the vagina then a pudendal nerve block is desirable A knowledge of this technique is useful although it rarely falls to the lot of the anaesthetist to perform it

The most commonly employed solutions used for injection are procaine 2 per cent and 0 5 per cent both combined with hyalase A fine bore 4-inch needle facilitates the placing of the analgesic fluid in the correct planes There are two methods of approach (1) The ischial spine is identified by palpation of the lateral wall of the vagina a wheal is raised with 2 per cent solution and the needle is advanced until the tip strikes the ischial spine it is withdrawn slightly and moved a little to the lateral side of the spine Five millilitres of 2 per cent solution are injected the needle being kept in constant motion The aim of the injection is to place the analgesic solution around the internal pudendal nerve as it passes into the perineum adjacent to the ischial spine It is maintained that infiltration of the tissues surrounding the levator ani muscles with 0 5 per cent solution relaxes the floor of the perineum This can be done as the needle is being withdrawn and if so desired up to 20 millilitres of 0 5 per cent procaine can be injected The internal pudendal nerve on the opposite side is blocked in the same way Local infiltration of the proposed site for episiotomy is thought to be advisable again with 0 5 per cent procaine solution (2) The alternative approach for the initial injection is externally at a point midway between the ischial tuberosity and the anus The direction of the needle towards the ischial spine is guided by two fingers in the vagina palpating the ischial spine

Caudal analgesia has been described at length by Galley and Peel in 1944 and Hingson and Edwards (1942) It has proved a very satisfactory method if applied to the right case at the right time of labour Galley s comprehensive survey of this technique emphasizes its value from the foetal point of view especially in

prematurity and in the presence of foetal distress (Galley, 1949) Epidural analgesia has, however, tended to supersede the caudal approach, since the introduction of the analgesic fluid at a point away from a potentially infected area is more acceptable to the obstetrician However, it must be admitted that the technique is more difficult and also the analgesia may need to be augmented by either a low caudal injection or a pudendal nerve block, since the sacral nerves 2, 3 and 4 may not be affected by the initial epidural injection

A fall in blood pressure may prove troublesome during these conduction techniques, especially if they are of the continuous variety Flowers (1954) recommends a continuous intravenous drip of 5 per cent glucose containing noradrenaline

In abnormal methods of delivery

Pudendal nerve block has already been described, and although a very satisfactory method it is sufficient only for limited manipulations The more extensive procedures demand greater areas of analgesia, and suitable procedures are (1) epidural block with or without pudendal nerve block or low caudal analgesia (2) caudal injection sufficiently high to block all nerves up to D 10 and (3) a subarachnoid injection The latter method is excellent for forceps delivery especially for the patient who has had a long and tiring labour when the clinical picture is often one of varying degrees of uterine inertia some dehydration distension of the abdomen in excess of the pregnant uterus and often the presence of foetal distress The result of the injection is most gratifying from both the patient s point of view and from that of the obstetrician Time is not lost and the patient can be placed in the lithotomy position immediately after the injection and the perineal and vaginal toilet commenced However, when the delivery is complete and the patient is changed from the lithotomy to dorsal posture, the blood pressure should be carefully observed lest it should fall unduly Whenever spinal analgesia is employed the manipulations of the obstetricians should be the minimal necessary since uterine activity can easily be stimulated and give rise to considerable difficulty with the delivery For breech delivery a saddle block is effective, and is usually performed with the patient in the sitting position between contractions Needless to say, it is useless for a breech extraction where only comparatively deep general anaesthesia can satisfy the requirements of both patient and obstetrician

Caesarean section presents a different problem since a fair proportion of patients in Great Britain prefer to be asleep throughout an abdominal operation It is undesirable to submit a patient to any method of conduction analgesia unless she is willing and the circumstances warrant it However, the mother is usually very co operative where the survival of her baby is concerned, and if she is promised anaesthesia after the infant is delivered she almost invariably agrees to the procedure The main points to remember are first the pregnant woman appears to need smaller doses of analgesic solution to produce the required level of analgesia secondly her blood pressure is extremely labile and a wise administrator has the necessary restoratives well at hand and thirdly satisfactory oxygenation of the maternal tissues should be maintained and where ventilation is impaired both by the uterus splinting the diaphragm and over enthusiastic analgesia oxygen should be given without delay Interesting observations on the mechanism

in sudden circulatory collapse during caesarean section have been made by Holmes (1957) He suggests that careful investigation of a patient showing circulatory instability may prevent catastrophe

The success of local infiltration for caesarean section depends mainly on the skill of the person performing the block A satisfactory technique has been described by Frankis Evans (1953) as the arrowhead block' It takes advantage of the fact that the somatic branches of the 10th, 11th, 12th dorsal and 1st lumbar nerves pass across the anterior axillary line, between the lower border of the 12th rib and the upper border of the iliac crest These blocks can if circumstances permit, be augmented at a suitable stage by thiopentone In all methods of conduction analgesia the operator should show tact and a high degree of skill if the procedure is to satisfy all concerned

Local techniques used therapeutically

Continuous epidural analgesia has appeared to give satisfactory results in reducing hypertension of toxaemia of pregnancy The reports of Hingson and Edwards (1943) and Ostlere (1952) have indicated success The renal function is improved and there is associated reduction in oedema

GENERAL ANAESTHESIA IN OBSTETRICS

There is a greater appreciation of the importance of the value of skilful anaesthesia in obstetrics and this advance has made a contribution to the improvement in the perinatal mortality over approximately the past two decades The success of inhalation anaesthesia in obstetrics depends mainly upon a smooth quick induction Satisfactory results can be produced by the skilful administration of cyclopropane or nitrous oxide and oxygen augmented by one of the volatile anaesthetics It is essential to ensure satisfactory oxygenation throughout the induction and main tenance periods of the operation If the patient is in active labour advantage can be taken of the increased inspiratory effort during a contraction, and any volatile anaesthetic being employed can be increased at that time If, however chloroform is being used the percentage must be increased with care Any method used should be judged as in analgesia according to its effect on mother, foetus and uterine activity It is essential that the drugs used should be effective in non toxic doses easily broken down and excreted with an absence of post operative ill effects since all anaesthetic and analgesic drugs given for systemic effect appear to pass the placental barrier (Apgar and Papper 1952)

That the obstetric patient is usually ill prepared for emergency anaesthesia is well known but since it is the practice in Great Britain to regard all labours as potentially normal unless abnormality has been detected in the antenatal period the patient s diet during labour is not favourable to anaesthesia A modified or totally fluid diet during labour is one way to curtail anaesthetic vomiting during delivery although Parker (1954) does not think that catastrophes are avoided entirely by administering purely liquid nourishment during labour He ascribes the asthmatic complication to inhalation of liquid vomit and the asphyxial type to aspiration of solid or semi solid food Various measures are being introduced to avoid this complication such as for example gastric lavage as a pre anaesthetic measure This is a practical method no doubt but one of little refinement, and

capable of reducing the blood oxygen to a dangerous level in a struggling patient, and undoubtedly creating an extra hazard for the foetus. A more recent method of reducing the incidence of vomiting is the administration of apomorphine before anaesthesia and is described by Holmes (1957). It appears to have some advantage over the previous measure, but still results in discomfort to the woman in labour. There is no doubt that one effective answer to pre-anaesthetic vomiting is a rapid smooth induction and a skilful anaesthetist can usually guide the patient to a safe level of anaesthesia. Cyclopropane is one of the most effective drugs, using as much as 50 per cent with oxygen until the patient has passed the danger level of vomiting and then reducing the percentage to a more normal value. Conduction analgesia is another satisfactory solution to the problem of vomiting during emergency obstetrical procedures.

Premedication

The two main needs are the control of salivation and the mental reassurance and support of the patient. Atropine 0.8 milligram ($\frac{1}{75}$ grain) given intravenously about 10 minutes before induction has, in the experience of the writer, proved highly satisfactory. The psychological aspect is too often ignored and the practice of placing the patient prematurely on the operating table and surrounding her with all the noise and bustle of preparation is all too common. Consequently the anaesthetist is presented with an apprehensive patient which to say the least is not conducive to the smooth induction which is all important. However the tranquillizers are contributing to this problem and in the writer's experience 4–5 millilitres of a combination of pethidine 100 milligrams, chlorpromazine 50 milligrams, promethazine 50 milligrams in 20 millilitres of solution injected intravenously about 15 minutes prior to anaesthesia provides a very satisfactory analgesia. In association with an epidural block it is very effective and if given before a general anaesthetic it does not appear to depress the infant.

Anaesthetic drugs

Most of the gaseous and volatile anaesthetics have been used in obstetrics. One of the more recently introduced members, methyl N propyl ether, is useful as it produces a quick induction (Sykes, 1949) and recovery is similarly rapid.

Dawkins (1950) recommended the administration of post-operative sedation before the patient leaves the table to avoid unpleasant sequelae. The use of intravenous barbiturates depends on the skill of the anaesthetist and his understanding of the effect of these drugs on the foetal respiratory system.

Relaxant drugs have made it possible for anaesthetists to provide a quiet field of operation for the obstetrician in abdominal delivery without the perils of deep anaesthesia (Gray, 1947; Davenport and Prime, 1950). Experimental work has indicated that these drugs do not pass the placental barrier or at least in quantities so small as to be ineffective (Young, 1949). Efficient ventilation of the maternal respiratory system is all important before the delivery of the infant but over-enthusiastic inflation is not to be recommended, since it may reduce the carbon dioxide in the maternal tissues to a very low level. Snyder and Rosenfeld (1937) found that hyperventilation of the maternal animal produced apnoea in the exposed rabbit foetus.

Halothane, the new non-explosive volatile anaesthetic, has been extensively

investigated from the point of view of general application (Medical Research Council, 1957), but further trials in the obstetric field are required

Intubation

The decision to intubate or not depends on the skill and wisdom of the anaesthetist Unless quickly performed it is better not to break the thread of the anaesthesia, except when there is a special indication A review of the opinion of the experts would reveal, in all probability, a fair division of opinion

Anaesthesia for procedures other than delivery

These patients should be given the usual care extended to general surgical cases but with the additional precaution of constant high oxygen intake The short acting relaxants are extremely useful in augmenting thiopentone for short manipulative procedures during pregnancy, for example external version If intra uterine conditions permit the turning of the infant, the thiopentone relaxant technique will improve the chances of success Manual removal of the placenta combined with heavy postpartum loss needs all the skill at the command of both obstetrician and anaesthetist Treatment of the inevitable shock is essential, although persistent bleeding may not allow the removal of the placenta to be delayed and the patient will be in a serious condition The anaesthetic level must be sufficiently deep to avoid further shock when the obstetrician introduces his hand into the uterus

CONCLUSION

The sphere of obstetric anaesthesia and analgesia carries an importance out of all proportion to its size and until this is appreciated by all anaesthetists the standard of anaesthesia will lag behind that of the other branches of the specialty It is the duty of the consultant anaesthetist to play a full part in the obstetrical service He should do all he can also by tuition and full support, to encourage the midwife so that she may be expert in obstetrical analgesia

REFERENCES

Apgar V and Papper E M (1952) *Curr Res Anesth* 31 1952
Bourne A W and Burn J H (1930) *Brit med J* 2 87
Bourne G (1954) *Lancet* 2 522
Cleland J G P (1933) *Surg Gynec Obstet* 57 51
Davenport H T and Prime F J (1950) *Brit med J* 1 1347
Dawkins M (1950) *Anaesthesia* 5 81
Dodek S M (1934) *Curr Res Anesth* 13 8
Dogliotti A M (1933) *Amer J Surg* 20 107
Embrey M P (1940) *J Obstet Gynaec Brit Emp* 47 371
Flowers C E Jr (1954) *Anaesthesia* 9 146
Frankis Evans T (1953) *Modern Practice in Anaesthesia* London Butterworth
Galley A H (1949) *Anaesthesia* 4 154
Galloway C E Grier R M and Blessing R (1936) *J Amer med Ass* 107 1707
Gray T C (1947) *Brit med J* 1 444
Hayward Butt J T (1957) *Lancet* 2 972
Helliwell P J and Hutton A M (1949) *Anaesthesia* 4 14
Hewer C L and Hadfield C F (1941) *Brit med J* 1 924

Hingson R A and Edwards W B (1942) *Curr Res Anesth* 21, 301
— — (1943) *J Amer med Ass* 123 538
Holmes F (1957) *J Obstet Gynaec Brit Emp* 2 229
Holmes J M (1957) *Proc R Soc Med* 50 556
Jackson D E (1934) *Curr Res Anesth* 13 198
Laborit H (1952) *Maroc méd* 330
Lund C J and Harris J W (1943) *Amer J Obstet Gynec* 45 980
MacDonald T J C (1950) *Brit J Anaes* 22 92
Medical Research Council (1954) Report No 30
— (1957) Report by the Committee on Non Explosive Anaesthetic Agents *Brit med J* 2 439
Nieschulz O Popendiker K and Sack K (1954) *Arzneimittel Forsch* 4 232
Norton H I Weingarten M and McDonough E T (1956) *Amer J Obstet Gynec* 71 1251
Ostlere G (1952) *Anaesthesia* 7 169
Parker R B (1954) *Brit med J* 2 65
Prescott F and Ransome S G (1947) *Lancet* 2 501
Randell O L and Lehmann C (1948) *J Pharmacol* 93 314
Reich A M (1951) *Amer J Obstet Gynec* 61 1263
Roberts Hilda (1948) *Brit med J* 2 590
— and Wrigley F (1953) *J Obstet Gynaec Brit Emp* 60 538
— Kane K M Percival N Snow P and Please N W (1957) *Lancet* 1 128
Schaffer A L (1956) *Amer J Obstet Gynec* 71 1247
Schlimpert H (1911) *Dtsch med Wschr* 37 719
Snyder F F and Rosenfeld M (1937) *Amer J Physiol* 119 153
Stoeckel W von (1909) *Zbl Gynak* 33 1
Sykes C E (1949) *Brit med J* 2 420
Walker J and Turnbull E D N (1953) *Lancet* 2 312
Wolff H G Hardy J P and Goodell H (1940) *J clin Invest* 19 659
Young I M (1949) *Lancet* 1 1052

CHAPTER 12

THE ANAESTHETIST IN THE PAEDIATRIC UNIT

G JACKSON REES

INTRODUCTION

PROGRESS in many fields of scientific activity is often made along a road which has been paved with a working hypothesis So it was in anaesthesia during the years following World War II when a concept evolved in which the state of anaesthesia was broken down into a number of components each of which it was thought possible to produce independently in varying degrees Thus individual patients might be brought into a state particularly appropriate to the proposed operation It was suggested that the state of anaesthesia involved a combination of narcosis muscular relaxation and analgesia (a term used for lack of a more appropriate word to imply a reduction of reflex response both autonomic and somatic to trauma) Based on such a concept there developed a technique of anaesthesia in which sleep was induced with a barbiturate, muscular relaxation achieved with a relaxant drug and analgesia was maintained with nitrous oxide, supplemented perhaps with pethidine or with minimal concentrations of a volatile agent

It was later suggested that to derive the optimal benefit from such a technique it was desirable to replace spontaneous respiration with artificial ventilation In this way the dosage of drugs required for the performance of any particular procedure could be reduced (Dundee 1952) Thus the concept of anaesthesia as a tetralogy of apnoea narcosis relaxation and analgesia was proposed (Rees and Gray 1952)

As a result of experience with the technique in which apnoea was maintained, it became apparent that patients in the relaxed and apnoeic state unconsciousness or amnesia (for under the pertaining conditions differentiation between these states is not possible) could be maintained by saturation of the patient with a 50 per cent concentration of nitrous oxide Thus the true place of nitrous oxide in anaesthesia became appreciated The role which it fills in such a technique is probably not dissimilar to the role of ether in the technique described by Artusio (1955)

These techniques were developed very largely in adult patients and there is reason to believe that this reflects sadly upon those engaged in paediatric anaesthesia for if such techniques are well adapted to the adult, they are much more applicable to the child

THE CHILD AS A SUBJECT FOR ANAESTHESIA

Cardio-respiratory considerations

The child must first be examined anatomically and physiologically as a subject for anaesthesia It is most profitable to consider the extreme of childhood that is the newborn infant and to compare him with the adult At birth the child is possessed of a heart which has hitherto had to provide a circulation through the body and through the placenta, a mass of tissue whose weight is considerable in relation to that of the child The capacity for work of the heart is reflected in its development In the child it is a relatively bigger organ than in the adult In infancy the cardio-thoracic ratio is 0 55, as compared with an upper limit of normality of 0 5 in adult life The functional reserve of the heart at birth is illustrated by the frequent absence of symptoms even in cases of gross structural abnormality At birth the heart is more than capable of performing its function

On the other hand it might be said that the functional efficiency of the respiratory system is minimal Up to the time of birth the lungs have not been functional and at birth their development is such that the area available for respiratory exchange is small both in relation to the weight of the child and to the size of the lung Engel s (1947) estimations of the area of the respiratory surface in relation to body weight shows it to be about 1,500 square centimetres per kilogram in adult life, whereas in infancy it is only about one third of this figure At the same time in infancy the oxygen consumption per kilogram has been shown to be much higher than in adult life some figures quoted give a value as great as twice that for the adult

It will thus be seen that the rate of gaseous exchange across the respiratory membrane of infants must be very high (about 6 times that of adults in basal conditions) This is facilitated by a high rate of ventilation exchange (3 5 litres per minute at 6 months) The effects of a relatively inadequate respiratory surface are seen in the periodic type of respiration which is so common in the newborn infant the cause of which is demonstrated by the fact that it is abolished by the exhibition of a high oxygen tension It is essentially similar to the periodic breathing seen in certain types of respiratory disease in adults and to the periodic breathing which results from respiring air at low atmospheric pressures in that the more highly efficient excretion of carbon dioxide is adequate with a small respiratory surface but oxygen uptake is not This being so the driving force of the respiratory mechanism is probably oxygen deficiency

These circumstances produce a demand for a relatively high respiratory minute volume The mechanism of pulmonary ventilation of the infant is possibly less efficient than that of the adult The relatively horizontal plane of the thoracic inlet and the configuration of the ribs cause respiration to be largely diaphragmatic The more complete dependence on diaphragmatic movement means a relatively greater shortening of its muscle fibres during inspiration This implies that the contraction deviates from the isometric and tends towards the isotonic a form of contraction in which tension is developed at the expense of very much greater oxygen consumption (Hill 1949) It has been suggested that these factors result in a high proportion of the total resting metabolism in infancy being used in the work of ventilating the lungs (Rees, 1954) This suggestion is supported by the

figures for oxygen consumption of the newborn before and after the onset of respiration.

Such considerations show how imperative it is that the work to be done in ventilating the lungs should not be increased by any anaesthetic technique, and that, in fact, it is desirable to reduce it if possible. The necessary conditions are readily obtainable if artificial ventilation is maintained and the work required for pulmonary ventilation is provided by an external source.

The achievement of controlled ventilation calls for endotracheal intubation and for the use of some myoneural blocking agent.

Endotracheal Intubation

In the past special hazards have been ascribed to instrumentation of the infant's larynx, but for many years most anaesthetists have regarded these hazards as another example of medical mythology. As long ago as 1922, Magill (Magill and Clausen 1925) expressed regret that the advantages of endotracheal intubation were not more frequently employed in paediatric anaesthesia, and in recent years in the American literature Smith (1953), Pender (1954) Pender and Hallberg (1953), and Eckenhoff (1951) have all reported very large series of cases in which intubation has been performed with a very low incidence of complications. At the Philadelphia Children's Hospital 98 per cent of all children under two weeks of age who are anaesthetized are intubated, as also are 65 per cent of all cases in all age groups (Eckenhoff, 1951). An endotracheal technique was used in virtually every case and no major complications resulting from this procedure had been seen.

Post intubation oedema used to be a real danger which has been eliminated by improvements in equipment and in preparation of the patient for intubation. Another contributory factor of importance is the better appreciation of the fluid and electrolyte requirements of children. In the past injudicious infusion of sodium chloride solutions was common but it is now appreciated that this inevitably and rapidly produces generalized oedema in infants especially noticeable on the dorsal aspect of the feet and hands. It is possible that many of the cases of so called post instrumentation laryngeal oedema may have been due to this cause.

Our predecessors had a particular horror of the use of endotracheal tubes in children with tracheobronchial infections, but it is now known that in many cases aspiration of the trachea and bronchi is a very valuable therapeutic measure. If therefore surgery is necessary for the relief of some acute condition in a child who is also suffering from a tracheobronchial infection it would be unreasonable to withhold aspiration which treatment endotracheal anaesthesia makes possible.

Furthermore the use of endotracheal intubation and controlled ventilation, with a muscle relaxant, will permit the maintenance of anaesthesia with nitrous oxide which is the least toxic of all anaesthetic agents known today.

Muscle relaxant drugs

The choice of muscle relaxants in children is generally speaking, governed by the same principles as in adults, and the sensitivity (weight for weight) appears to be similar.

The newly born infant however is in this respect exceptional. The expression 'newly born' has been used here deliberately as it does not imply a definite age

range as does the term neonatal For a variable period following birth the infant appears to be peculiarly sensitive to the action of myoneural blocking agents of the antidepolarizing type and to be resistant to depolarizing effects (Stead 1955) This type of response does not persist beyond the first three or four weeks of life, and is interesting when considered in relation to other changes in the infant s make up occurring at the same time

An investigation by Rickham (1957) of the metabolic responses to trauma of the newly born has shown that all infants exhibit, as do adults, a negative nitrogen and potassium balance following surgery In the case of the infant, however, the quantitative relationship between the loss of potassium and the loss of nitrogen is different In the adult the ratio between the loss of nitrogen and that of potassium is higher than that in which the two elements exist in lean muscle tissue This is taken to indicate that besides a breakdown of tissue which liberates potassium and nitrogen there is also a loss of potassium from cells which do not break down and lose their nitrogenous content On the other hand in the newborn infant the metabolic response to surgery is such that the potassium/nitrogen ratio approximates to the ratio in lean muscle tissue, indicating that, although there is a breakdown of tissue there is no loss of potassium from those cells which retain their nitrogen

It is interesting to speculate whether there might be a relationship between this absence of the pathological diffusion of cations across the cell membrane, and, on the one hand, the ease with which the physiological diffusion of these ions associated with muscular activity may be inhibited by antidepolarizing agents and on the other the apparent resistance to drugs, the action of which is dependent upon the production of cation diffusion—the depolarizing drugs

There is another feature of the response in early life to the relaxant drugs which is frequently seen The so called dual response' to suxamethonium is very much more obvious in newly born infants, and almost invariably the maintenance of relaxation with the drug for any length of time will result in some residual paralysis This paralysis may be reversed with edrophonium it is greatly exaggerated if ether has been administered in combination with the relaxant A further point is that muscular fasciculation is not seen following the injection of suxamethonium in the very young These features are perhaps not unexpected in the case of a patient whose response to antidepolarizing agents is marked and to depolarizing agents is relatively slight

The response of patients in this age group to relaxant drugs is thus similar to that of the patient with myasthenia gravis This might be considered in relation to the discovery of Wilson, Obrist and Wilson (1953) that extracts of foetal thymus and of the thymus glands removed from myasthenic patients are both capable of influencing myoneural transmission There also seems to be some possibility that there is a common cause for the behaviour of the newborn and of the myasthenic patient in response to relaxant drugs, and for the difference between the metabolic response to trauma between the infant and the normal adult It may be that the response to trauma of the myasthenic patient may approximate that of the infant, and it is considered that there is room for investigation of this possibility

Whatever may be the cause of the sensitivity of the very young to anti polarizing drugs, it would seem sufficient to discourage their use in these patients, and there is a growing tendency to use instead intermittent doses of suxamethonium

The responses to these drugs appear to assume the adult pattern quite early in life, and at the end of the neonatal period the antidepolarizing drugs may be given in doses equivalent (weight for weight) to those used in adult patients

Hyperpyrexia

As has been suggested, consideration of the infant or child as a subject for anaesthesia suggests that he is well adapted to the current 'apnoeic techniques of anaesthesia The truth of this is perhaps most dramatically illustrated by the temperature changes which occur under anaesthesia of this type

A common and feared complication of anaesthesia in children was formerly hyperpyrexia often leading to convulsions and to death This complication was most common in the age groups from three or four years to seven or eight years, and is rarely seen in infants under about six months, whose temperatures tend to fall rather than rise under all types of anaesthesia

A variety of aetiological factors have been suggested and include carbon dioxide retention, respiratory obstruction, atropine premedication, dehydration, pre operative infection, mackintosh drapes and ether anaesthesia The condition is seen classically in the dehydrated and pyrexial child with peritonitis, and in the past it was suggested that the administration of atropine to such children as part of their pre operative premedication predisposed to the development of hyper pyrexia In the author s experience these patients always show a fall in body temperature when anaesthetized by a technique which includes control of the respiration, even though atropine is invariably given pre operatively These views are expressed as a result of experience gained in a temperate climate (Great Britain) and where hyperpyrexia, although encountered in the past has not been so frequent or as serious a complication as in those regions where higher tempera tures are encountered However, those series of cases which have been reported from such regions invariably have been anaesthetized by a technique in which the respiration has been spontaneous There is a need for an investigation in a warm climate into the relative incidence of hyperpyrexia after anaesthesia by techniques in which respiration is, on the one hand, spontaneous and, on the other controlled

Premedication

In the past there has been a strong body of opinion that children should be prepared for anaesthesia in such a way that they are asleep on reaching the operating theatre It can be argued with some truth, that such a view is based on an unenlightened approach to the problems of life which face the child a keener appreciation of which in recent years has been reflected in many diverse aspects of child management The concept of the mother and young child as a single bio logical unit the disruption of which is liable to produce in the child at best a period of profound misery, and at worse a life long effect on his behaviour pattern has led to the belief that in many cases of child neglect it is better to maintain the family unit than to place the children in the care of the local authority The aphorism that a bad home is better than no home at all has much to commend it A parallel line of thought has led to the view that it is desirable for the child in hospital to be visited daily despite the reactionary opposition in some quarters on the grounds that it upsets the child just when he is settling down This settling down process is in fact a retirement of the child into himself,

and the development of apathy This can often be appreciated by the sympathetic observer even in the best paediatric units The daily reassurance that a visit from his mother gives to the child is more than compensation for the outburst of emotion which may follow her departure

The question of the state which it is desirable to induce with the premedication given to a child should be considered in the light of the child s great fear of abandonment It is moreover, clearly undesirable that there should be a period of recovery in which there is a prolonged twilight state, possibly with restlessness induced by post operative pain and in which the mental state is such that contact with the child cannot be made It would appear much more desirable that he should be conscious pre operatively, so that before and while anaesthesia is being induced, he can be assured of the anxiety which mother (or the mother substitute according to social background) is feeling, and that he should recover rapidly from his anaesthesia to the reinforcement of these suggestions, preferably by the same individual

Regarded in this light it would appear that the oral barbiturates if used in dosage sufficient to produce pre operative unconsciousness, would probably be bad in their psychological effects This was illustrated to the author by the train of events in an ear, nose and throat unit with a large turnover of tonsillectomies A new anaesthetist introduced as premedication heavy dosage of quinalbarbitone This was followed by a remarkable increase in the incidence of post operative night terrors which was again reduced when the policy of pre operative unconsciousness was abandoned

These matters require further investigation, but in the meantime it is well to appreciate that the psychic trauma of the operation is not necessarily eliminated because the child is unconscious on reaching the operating theatre

The real danger of such trauma is very much less in those children whose emotional developmental age is greater than five years (this does not necessarily parallel the chronological or intellectual age), and it is wise not to perform surgical procedures, which are not urgent, on children who have not reached such a stage of development

It would seem that the ideal state to induce pre operatively is one in which the child is conscious amenable to suggestion and is sufficiently analgesic to minimize the pain of intravenous induction This may be achieved with a small dose of oral barbiturate combined with morphine or some other analgesic on a dose for weight scale with a phenothiazine derivative alone or in combination with an additional analgesic, or with one of the newer tranquillizers

ANAESTHETIC APPARATUS AND THE CHILD

The dead space

The design of anaesthetic apparatus for children has not always been intelligent, and there has been a tendency in the past towards 'miniaturization , that is towards the scaling down of apparatus designed for the adult patient It is felt that such attempts are doomed to failure because they do not take cognisance of the high respiratory rates seen in children If the total minute volume is to remain constant a proportional increase in the dead space will reduce the effective ventilation more profoundly than if this minute volume were achieved by a lower

rate. Thus, if anaesthetic apparatus which possesses a dead space acceptable in the adult is scaled down in size to the proportions of an infant patient, the dead space of the reduced apparatus is not necessarily acceptable for the child. Efforts to reduce the dead space of anaesthetic apparatus for children have led in the North American countries to the development of non-rebreathing valves and in Great Britain to the adoption of various modifications of the Ayres T-piece.

Reduction of rebreathing

The non-rebreathing valves have a measurable dead space, which, in the case of the Slater-Stephens valve, is approximately 10 millilitres. The degree of rebreathing in the Ayres T-piece is rather less easily definable, and presents a complex problem. Formerly it was considered necessary to adjust the capacity of the expiratory limb of the T-piece, but more recently there has been a tendency to neglect this, maintaining a length which is in excess of the tidal volume, and to adjust the flow rate of fresh gases to minimize rebreathing. The necessary flow of fresh gases in T-piece circuits has been estimated mathematically (Mapleson, 1954) and by experimental methods using an artificial lung (Inkster, 1956). The general conclusions of such investigations suggest that provided the minute flow rate of fresh gases into a T-piece system is about twice the respiratory minute volume there is no significant rebreathing. The precise value for the relationship between the rebreathing percentage and the tidal volume in these T-piece systems varies with the form of the respiratory curve, being less if this is of the type in which there is a pause in expiration. The T-piece may be adapted for artificial ventilation if some means is provided of varying the pressure at the outflow point. This may be done by intermittent occlusion of the outflow or, better, by fitting to the outflow a double-ended reservoir bag, through which the gases escape to the atmosphere and which may be used as a means of controlling respiration if the outflow is restricted (Rees, 1950).

Carbon dioxide absorption

There would appear to be a current trend away from carbon dioxide absorption methods in all types of anaesthesia, a trend which possibly is the result of better understanding of the principles of the semi-open circuits, and possibly due to the diminution in the use of cyclopropane. In paediatric practice the classical virtues of carbon dioxide absorption methods, namely conservation of gases, conservation of heat and conservation of water vapour, are less obvious, because the flow rates required on semi-open circuits are small and because heat loss should not be discouraged. Water vapour can be efficiently added to the gases by a humidifier if this is considered to be desirable. Moreover, it is difficult to arrange a Waters type of canister on the smaller infants in such a way that the dead space is negligible. Although it is felt that there is little place for circle absorbers in smaller children, over the age of four or five years carbon dioxide absorption may be useful, as at this age the minute volume of the child is such that high flow rates are required in semi-open circuits.

Inhalation apparatus of the type described by Picken (1950) and Swerdlow (1956) in which the gas flow from the anaesthetic apparatus is connected to the endotracheal tube with an intervention of a perforated brass tube, the perforations in which are open to the atmosphere, has the disadvantage that should the rate

of inspiration exceed the rate of gas flow the anaesthetic gases are diluted with atmospheric air This would seem to be a serious deficiency if the technique is one in which nitrous oxide is to be used as the only narcotic agent

Size of rebreathing bag

No discussion on inhalation anaesthetic apparatus is complete without mention of the effect of varying the size of the rebreathing bag when this is used to produce intermittent positive pressure ventilation Manual compression of such a bag increases the tension of the rubber membrane, and it is the tension set up which produces the increase in pressure within the bag The pressure difference set up between two sides of a spherical membrane in tension varies inversely with the diameter of the sphere It follows that for any given degree of muscular effort on the part of the anaesthetist the pressure produced within the bag will be greater if the bag is small The pressures required to ventilate children of varying ages are the same as, or greater than, those required to ventilate adults Therefore, if the size of the bag is matched to the size of the child, less muscular effort is required for adequate ventilation in the smaller children This is a considerable advantage, because it enables the operator to appreciate more accurately the pressure and volume changes occurring with each inflation of the lungs, factors which are very much more difficult to assess with a large bag if the tidal volumes are small

INTRAVENOUS TECHNIQUES IN CHILDREN

The increasing use of intravenous drugs in paediatric anaesthetic practice has called for the development of reliable methods of gaining access to the blood stream The practice of giving intravenous infusions into the scalp veins of infants has helped considerably Available for this purpose are special needles with a nozzle at their proximal ends which may be inserted into a fine polythene tube to take a Record or Luer adapter These scalp drips may be fixed in position with narrow strips of plaster bandage or with one of the plastic skin dressings, and they will run satisfactorily for long periods The scalp veins may also be used for direct injection of drugs, but even here the hazard of intra arterial injection is not absent The author has on two occasions seen the injection of thiopentone into the superficial temporal artery or one of its branches In neither case did any permanent damage result (a 2 5 per cent solution of the drug was used in both cases) In one the volume injected was a fraction of a millilitre and the effect was a transient blanching of an area of the scalp in the other case 2 millilitres were injected and this resulted in impairment of the circulation in the scalp for several days but there was no skin necrosis This accident should not occur if the precaution is taken of palpating the vessel prior to puncture

For major surgical procedures and when it is felt that blood transfusion may be necessary the scalp drip should be considered inadequate, and a polythene cannula should be inserted in a leg vein In infants, if the drip is to be used as a route for the injection of drugs, it is useless to make the injection into the rubber tubing where it will be diluted with an indeterminate volume of fluid and enter the circulation at a rate and time which will be governed by the rate at which the infusion is running usually very slowly Direct injection of drugs should be the

aim, and this can be achieved only by the use of a three-way tap fitted to the end of the polythene cannula

For direct injection into the venous system of infants whose growth of hair precludes the use of the scalp vein, the wrist provides the most promising site In small children a needle of suitable size (20 or 27 gauge) may be allowed to remain as an indwelling needle There is little tendency for reflux of blood and clotting to occur, after the injection of drugs along the course of these thin walled veins there is often a local wheal produced, which slightly raises tissue tension locally and thus prevents the reflux of blood Intravenous techniques in children over the age of three or four years present no special problems

THE PAEDIATRIC ANAESTHETIST AND PULMONARY DISEASE

In smaller children the risk of post operative pulmonary complications is greater than in adults and older children, and, furthermore, the pattern of such complications is rather different If an adult patient has a post operative lobar collapse, it is almost invariably the lower lobe which is affected, but in infancy it is much more commonly an upper lobe The reason for this is possibly to be found in the difference in anatomy of the chest wall in infancy, when the ribs and the angle of the thoracic inlet are relatively horizontal This necessarily means that, with spontaneous respiration, ventilation of the upper lobe is less efficient than in the adult There is *in addition a difference in the configuration of the* bronchial tree in that, in infancy, the upper lobe bronchi pass more directly backwards than in the adult, they are thus more likely to become flooded if fluids are aspirated into the bronchial tree

Whatever may be the reason, when a partial collapse occurs in the lung the upper lobe is usually affected first and recovers last It is, therefore, essential to nurse all infants post operatively with a head up tilt Total collapse of a lung is common in the newborn following operation, and particularly so in premature infants It is usually possible to re expand these lungs by posturing the child with the affected lung uppermost, and by light tapping of the chest It is not uncommon for such treatment to re expand the affected lung completely while resulting in the total collapse of the contralateral lung Such alternating collapse of a lung may occur several times in one child Fig 24 shows the serial radiographs of a child in the post operative days following repair of oesophageal atresia

If posture does not result in re expansion of the lung it is necessary to treat the *condition more actively In the case of the right lung, fluid aspiration with a soft* catheter is usually effective but in the case of the left lung bronchoscopy is frequently required

Apart from the head up position the neonate may be protected from post operative pulmonary complications by being nursed in an atmosphere of high humidity This is best achieved by the use of one of the excellent infant incubators which are now available and which permit the regulation of the temperature and humidity of the child s environment Humidification of the atmosphere for older children is best carried out with an atomizer Good results are claimed for detergent solutions such as Alevaire which may be used in atomizers to facilitate the coughing up of secretion, but it is doubtful whether these have any advantage over droplets of water (Palmer, 1957)

(a)

(b)

(c)

FIG 24—Radiographs of infant aged two days following operation for repair of oesophageal atresia and showing alternating collapse and expansion of lungs (a) Right lung expanded—left lung collapsed (b) Right lung collapsed—left lung expanding (c) Right lung expanding—left lung expanded

After thoracotomy young infants exhibit a grunting type of respiration, holding the breath momentarily in inspiration This is probably caused by painful stimuli arising from the operative site, for it is abolished by analgesic drugs After such drugs the ventilation is better and it is believed that their use even in the smallest infants reduces the incidence of pulmonary complications and assists in their resolution

It is essential, if the mortality rate is to be low, that any unit where major surgery is carried out on young infants should be equipped for the treatment of respiratory emergencies An emergency trolley equipped with suction apparatus, laryngoscopes, bronchoscopes endotracheal tubes and suction catheters should be available for immediate use, and there must be resident staff available who are capable of dealing with such emergencies when they arise

Apart from the post operative pulmonary complications there is in the paediatric hospital a wide field open to the anaesthetist interested in respirology The application of anaesthetic methods to many of the acute respiratory diseases of children can often be life saving The epidemic bronchopneumonia of infancy with copious secretions is frequently an indication for emergency tracheobronchial toilet, and, as the cause of death in this condition is often a primary respiratory failure, resuscitation by means of artificial intermittent positive pressure ventilation is sometimes possible

The acute membranous laryngotracheal bronchitis is another condition to which anaesthetic management is applicable In this condition there forms within the bronchial tree a thick membrane usually of a dark colour consisting of inspissated mucopus and necrotic epithelium The membrane may become detached in places and cause respiratory obstruction and death Treatment is normally by tracheotomy and removal of as much debris as possible, but in spite of this the condition is often fatal As in all cases of respiratory obstruction there occurs the vicious cycle of inadequate ventilation leading to increased metabolism and so to increase in the ventilation demand It has been customary in the past for the tracheotomy to be performed under local anaesthesia, a procedure which in the circumstances would seem unnecessarily discomforting and irrational The obvious anaesthetic approach to such a case would be to anaesthetize the child either with nitrous oxide which is usually quite feasible in the presence of the carbon dioxide accumulation which will exist in a severe case or with a minimal dose of intra venous barbiturate, and to abolish respiratory muscular activity with a relaxant drug In this way the metabolic demands are reduced and ventilation may be carried out by intermittent positive pressure respiration This artificial ventilation will result in a larger tidal volume because the inspiratory phase may be prolonged as compared to the brief inspiratory phase of the tachypnoea which exists as a result of the obstruction A short period of such ventilation either with an anaesthetic face piece or an endotracheal tube will permit a more leisurely bronchoscopy During such a bronchoscopy ventilation may be continued by fitting an endotracheal tube into the lumen of the bronchoscope

In many of these patients the state of the larynx makes it impossible to pass a bronchoscope in which case resuscitation is maintained with a face piece or endotracheal tube while a tracheotomy is established Thereafter a per tracheotomy bronchoscopy may be performed The condition is one which taxes the ingenuity of the anaesthetist but one in which the intelligent application of modern anaesthetic methods can often be lifesaving

ANAESTHETIC METHODS IN THE TREATMENT OF THE DISEASED CHILD

Tetanus

Anaesthetic methods may be applied to the treatment of tetanus in even the youngest children one case of neonatal tetanus was maintained under the influence of relaxant drugs and on intermittent positive pressure respiration for as long as 34 days As regards the place of tracheotomy the approach to such cases may vary from the accepted practice in adult cases In the smallest infants tracheotomy is difficult to manage because of the relatively large head and relatively small neck, furthermore, the small distance between the stoma and carina makes it very difficult to provide an airtight seal between the tracheotomy tube and the trachea when positive pressure ventilation is used In spite of the general view of the difficulty in managing tracheotomies in infancy, there is a Scandinavian unit in which tracheotomy is performed routinely in all cases of oesophageal atresia The author has always felt that, when it is desirable to maintain continuous artificial ventilation in infancy for long periods, it is preferable to use endotracheal tubes until a stage is reached when reversion to spontaneous respiration is possible, or at that stage to perform tracheotomy if necessary

Salicylate poisoning

The place of anaesthetic methods in the treatment of poisoning with narcotic drugs in children is established, but among the commonest drugs responsible for accidental poisoning in childhood are the salicylates (It is estimated that in the United States of America 86 children under five years of age die annually from salicylate poisoning) The most common, alarming and lethal manifestation of intoxication with these drugs is hyperventilation This is brought about by an effect on the nervous mechanism of respiration, and leads to widespread bio chemical changes and death There has been a recent report of this condition being treated by the use of relaxant drugs to paralyse the hyperactive respiratory muscles and by artificial ventilation until such time as the blood level of the drug fell to a harmless value It would seem that the application of such a line of treatment might lower very considerably the mortality from salicylate poisoning (Freier and his colleagues, 1957)

RESUSCITATION OF THE NEWBORN

Classification of conditions

An aspect of paediatrics which is within the province of the anaesthetist is resuscitation of the newborn To review this problem it is necessary to classify the conditions which produce the need for resuscitation It is possible to divide them into two main groups as follows failure of respiratory effort and failure to ventilate despite respiratory effort

Group I failure of respiratory effort

In this group must be included all those infants who fail to breathe at birth because of damage to, or insufficiency of, the nervous mechanism of respiration This may be due to drugs anoxia, cerebral trauma, or immaturity

Group 2 failure to ventilate despite respiratory effort

This group consists of those infants who have respiratory obstruction which may be the result of postchoanal atresia, micrognathia, congenital tracheal stenosis or atresia, foreign matter in the bronchial tree intrathoracic tumour or diaphragmatic hernia In this group there should also be included another type of respiratory embarrassment which is also, in effect, a respiratory obstruction This occurs when pulmonary development in the premature infant has not yet reached such a stage as to be capable of expansion

In attempting to subdivide the infants with respiratory difficulty into these two groups it must be appreciated that an infant in group 2 (the obstructive group) might secondarily have an anoxic failure of the respiratory centre

Treatment

The methods available for the treatment of these conditions are also divisible in two groups

(1) Attempts to supplement the oxygenation in the lungs by intragastric oxygen

(2) Methods of augmenting pulmonary ventilation

Methods of artificial ventilation are (a) by intermittent positive pressure, (b) by rocking (c) by a Drinker type of respirator, which may be triggered by the patient and (d) by electrophrenic stimulation

The commonsense approach to the selection of the treatment for group 1 cases is to supplement the pulmonary ventilation and it is felt that in such cases there is no place for intragastric oxygen therapy The most efficient form of therapy is by endotracheal intubation and intermittent positive pressure ventilation The other methods of supplementary ventilation are less efficient but may be carried out by relatively unskilled personnel

In the obstructive group of cases the treatment should, where possible, be directed towards the relief of the obstruction, and in most cases this may again be effected by endotracheal intubation and intermittent positive pressure respiration

The most difficult group consists of those infants who are of such prematurity that, despite quite powerful respiratory efforts, little or no ventilation is achieved because the lung has not as yet developed sufficient air spaces to permit expansion It is in this group that there may be a place for intragastric oxygen It has been suggested that attempts to ventilate the lungs by positive pressure may result in rupture of the lung and surgical emphysema However, the forces which the infant is capable of developing by his own respiratory efforts are such that rupture and emphysema may occur spontaneously and the pressure likely to be used in resuscitation is unlikely to produce damage if it does not exceed 25 centimetres of water It is the author s view that even this group of infants is better treated by assisted ventilation

REFERENCES

Artusio J F (1955) *J Amer med Ass* 157 33
Dundee J W (1952) *Brit med J* 2 893
Eckenhoff J E (1951) *Anesthesiology* 12 401
Engel S (1947) *The Child s Lung* London Arnold
Freier S Neal B W Nisbet H I A Rees G J and Wilson F (1957) *Brit med J* 1 1333
Hill A V (1949) *Proc roy Soc* B136 211

REFERENCES

Inkster J S (1956) *Brit J Anaesth* 28 512
Magill I W and Clausen R J (1925) *Proc R Soc Med* 19 8
Mapleson W W (1954) *Brit J Anaesth* 26 323
Palmer K N V (1957) *Lancet* 1 611
Pender J W (1954) *Anesthesiology* 15 495
— and Hallberg O E (1953) *J Amer med Ass* 153 1073
Picken D (1950) *Brit med J* 1 954
Rees G J (1950) *Brit med J* 2 1419
— (1954) *Brit J Anaesth* 26 154
— and Gray T C (1952) *Brit med J* 2 891
Rickham P P (1957) *The Metabolic Response to Neonatal Surgery* Cambridge Mass, Harvard University Press
Smith R M (1953) *Curr Res Anesth* 32 102
Stead A L (1955) *Brit J Anaesth* 27 124
Swerdlow M (1956) *Brit J Anaesth* 28 340
Wilson A Obrist A R, and Wilson H (1953) *Lancet* 2 368

CHAPTER 13

THE PITUITARY ADRENAL SYSTEM AND ANAESTHESIA

E. F. SCOWEN

THE GENERAL ADAPTATION SYNDROME

THE CONCEPTION of systemic stress and the general reactions which occur in response to such a stimulus we owe to Selye (1937, 1944), from whose original animal work the concept of the general adaptation syndrome has been elaborated (Selye, 1946, Albright 1943a and b, Ingle 1942). Nomenclature has caused much confusion and in order to consider the behaviour of the pituitary and adrenal glands it will be necessary to consider briefly the general adaptation syndrome and its component features. Not only to the surgeon is the recognition of these components of basic importance, but also to the anaesthetist, who has to face the stress response of his medication and the superimposed stress of surgical trauma. Upon the anaesthetist also rests the responsibility of assessing the effects of previous stress before anaesthesia is undertaken.

The general adaptation syndrome consists of three main phases: (1) the alarm reaction, (2) the stage of resistance, and (3) the stage of exhaustion.

The alarm reaction

The alarm reaction is characterized by all the non specific phenomena which occur in response to the sudden exposure of large portions of the body to damaging stimuli: traumatic, chemical, physical or emotional. This deviation from the normal resting state of extensive somatic areas either because of a functional or direct injury constitutes systemic stress, and the agent responsible is designated the stressor. If the stressor be applied acutely it is the alarming stimulus which will alert the alarm reaction, and if the action be prolonged, will initiate the whole sequence of the general adaptation syndrome. It will become apparent in the later stages of the syndrome that the full characters of the alarm reaction can be produced only if the organism be not adapted to the stressor used.

The alarm reaction can be divided into two phases: the phase of shock and the phase of counter shock.

The shock phase

The phase of shock represents the sum total of the tissue damage and is characterized by a fall in body temperature and of the blood pressure, depression of the central nervous system and a decrease in muscle tone. There is a marked disturbance of cell membrane permeability with haemoconcentration, hypochloraemia, a rise in the blood potassium and sometimes acidosis. There is an

excessive tissue breakdown and hence a loss of nitrogen (Engel, 1951, Cuthbertson, 1932)

The counter shock phase

The phase of shock is always followed by the phase of counter shock, unless the damage is too severe and death occurs It is characterized by the reversal of many of the changes seen in the phase of shock Pyrexia with a rise in the blood pressure and blood volume develops The blood chlorides and blood sugar rise (Sprague and his colleagues, 1950) There is a tendency to alkalosis and there may be a diuresis In many circumstances there is a leucocytosis although there is a marked blood eosinopenia During this phase there is a marked tendency to the development of gastric erosions and gastro intestinal haemorrhage

The importance of these stages of the alarm reaction must be emphasized for they are the essential changes in the non specific recovery from systemic stress and the same train of events can be set in motion by a bewildering variety of agents On this basic pattern therefore there will be superimposed the direct actions of the stressor which may confuse the picture The syndrome may thus be modified by a number of factors or conditioning factors , which include the direct pharmacological action of the stressor, the state of receptivity of the target organs and the general state of the whole body in relation to its nutrition and to recent and previous similar or diverse stress reactions

The stage of resistance

The simple sequence of shock and counter shock represents the recovery from short sub lethal systemic stress If however, the stress is prolonged or repetitive the body becomes inured or has acquired adaptation It becomes more difficult to produce an alarm reaction by the same stressor This is designated the phase of resistance It seems probable that, in many circumstances this protection is gained at the expense of decreasing resistance to different stressors The body changes both biochemical and morphological which occur in this phase are negligible but may show a tendency to overswing from the changes of shock

The stage of exhaustion

However perfect adaptation may appear the stage of resistance to continuous or repeated stress exposure cannot be maintained indefinitely The extent of the resistance is finite and individual and constitutes what is called the adaptation energy This energy appears to depend largely on genetic factors and though it may be modified to some degree by changes in nutrition it cannot be changed to any marked degree

If therefore stress continues and resistance is overcome all the changes of the shock phase return and further resistance is impossible counter shock does not occur The changes become irreversible and death will ensue This represents the phase of exhaustion

Such are the features and sequence of the various stages in recovery or death from systemic stress They are the same whatever the stresses and the whole represents the general adaptation syndrome The diverse features which may be superimposed mainly occur when conditioning factors for example a general anaesthetic modify the syndrome by their special pharmacological actions Let

it be emphasized that recovery from this action still demands the same sequence of general non specific reactions whatever specific actions may be needed for the eradication, metabolism or detoxication of the agent used

ADRENAL FUNCTION ADAPTATION

The fundamental changes in the body which occur in response to and recovery from stress are still largely unknown It is, however certain that the adrenal response is essential to recovery from stress (Engel, 1953) It is equally certain that, unless an adequate response occurs or adrenocortical hormones are supplied in adequate amounts recovery will not occur (Hardy and Ravdin, 1952, Moore and Ball, 1952)

The activity of the adrenal gland is produced by stimulation with corticotrophin released from the anterior pituitary gland The vital reaction therefore is the *mechanism which brings about an immediate and sufficient output of cortico* trophin (Ingle, 1951, Long 1950 Engel, 1953)

Factors influencing release of corticotrophin

Animal experiments show that there are at least two factors which may be responsible for release of corticotrophin, nervous and humoral It is difficult at present in man to separate these factors and indeed with increasing knowledge of humoral factors in nerve transmission the distinction may be artificial But the response to a nervous impulse may be much quicker than the humoral response (Fortier, 1951, Hume 1953)

The response to adrenaline, which is always released in the alarm reaction may also play a part in corticotrophin release Indeed, this response has been used as a measure of the adequacy of the pituitary and adrenal functional reserve mainly by estimating the resulting eosinopenia (Recant and his colleagues 1950 Wolfson, 1953 Farrell and McCann, 1952)

There remains one aspect, which has received insufficient attention It is certain that the pituitary gland can release corticotrophin in response to humoral factors It seems reasonably certain that, at least within certain limits one of the main controls of regulation of corticotrophin release is the level of circulating adrenal corticoids We know that adrenal hyperplasia can be prevented by adequate cortisone administration indeed adrenal atrophy can be induced We know, also that this effect of cortisone can be lessened or overcome by the concomitant use of corticotrophin The blood levels of corticotrophin can be shown to be increased in Addison s disease and in congenital adrenal hyperplasia (Sydnor *and his colleagues 1953) and some functional adrenal tumours may induce* atrophy of the normal adrenal tissue

After hypophysectomy adrenal atrophy occurs This atrophy can be repaired or prevented by corticotrophin It is of interest that this repair will occur regardless of the quantity of cortisone administered The adrenal failure induced by hypo physectomy differs from the effects of total adrenal ablation by surgery or disease and it is now known that after hypophysectomy some residual function persists in the adrenal gland Elaboration of corticoids ceases but some aldosterone

production continues which enables more stability to be maintained in electrolyte balance than is the case after adrenalectomy Present evidence suggests that aldosterone production is in fact autonomous, although an increase can certainly occur in response to adrenal stimulation

Circulatory corticoids

If the rapid reduction of circulatory corticoids is in any measure responsible for the rapid corticotrophin release in the alarm reaction, then there must be a rapid utilization or removal of such substances from the blood The need for them in recovery from stress is both aggravated and pressing Amounts are released and metabolized, which under normal conditions would rapidly produce signs of overdosage and mimic the manifestations of Cushing s syndrome During this phase large amounts of corticoids can be administered without untoward effects in fact it is really astounding at times how much can be given with only good effect

Clearly there is need for a great increase in corticoids and they are removed and metabolized rapidly If the increased demand is not met adequately, then manifestations of adrenal failure may occur even though at that time the corticoid production is well above normal Normal obviously in the stress response and recovery is multiplied many times from resting normal Since large quantities are removed so quickly, it is easy to understand how much more quickly—and it must be almost instantaneously—the small circulating quantity of the resting normal will disappear when the increased demand is made

To apply the information which we now possess in clinical practice demands that it should be possible to measure the reserve capacity of this vital reaction to stress For with adequate reserve no interference will be necessary provided the stress is not overwhelming or too protracted At present no satisfactory method which can supply this need is available

Two methods have been tried The first is the eosinopenic response to an injection of adrenaline At this stage no advantage can be gained by a discussion of this test for there is increasing doubt about its reliability

There is no other method to test pituitary sensitivity, but corticotrophin can be used to test adrenocortical reserve (Thorn and his colleagues 1948) Intramuscular injection is unreliable and the injection must be given intravenously This necessitates an intravenous administration over eight hours and a measurement over this time of the eosinopenic response, and the increase in corticoids and 17 ketosteroids in the urine over at least 24 hours—a cumbersome and tedious test at best and demanding elaborate laboratory facilities It is unsuitable for routine use

Assessment of the adaptation phase

For the assessment of the adaptation phase and the reserve of energy that remains we are left only clinical judgement It is this which demands a full awareness and understanding of the whole adaptation complex as a necessary preliminary to the clinical assessment

If the present state of the patient be understood in this perspective any features suggesting adrenal hypofunction obviously must be viewed with grave suspicion

It will be well to recall, also that the amount of adaptation energy is largely genetically determined but nutrition at the time can enhance or detract from this Finally there is a suggestion that the total 17 ketosteroid output declines progressively if repeated stresses invoke major adrenal reactions and that full recovery of adrenal energy may take many months, and it is doubtful whether in some instances a full recovery of energy reserve can ever occur (Hardy, Richardson and Dohan 1953, Moore and Ball 1952, Hardy and Cole, 1953)

THE PRE-OPERATIVE AND POST OPERATIVE USE OF CORTISONE

The preceding discussion makes it abundantly clear how vital to recovery from anaesthesia and surgical operation is the adrenal response An example of the method of using cortisone to mimic the normal reaction is provided by surgical operation for the removal of the adrenal or the pituitary gland The pioneer work of Huggins (Huggins and Bergenstal 1951 1952) was hampered by inadequate maintenance but the introduction of cortisone and later compounds has made possible the expansion of this type of operation during the last five years (Luft Olivecrona and Sjogren 1952 Luft and Olivecrona 1953 1955, 1957, Luft and his colleagues 1956, Pearson and his colleagues, 1953 1955, Pearson 1956, Pearson and his colleagues 1956 Ray and Pearson 1956)

The initial demand for increased corticoids will begin concomitantly with anaesthesia and the early operative stages reaching its maximum within a few hours This maximum level will be required for two to three days and then the demand will gradually decline, in the absence of complications to a normal maintenance level within seven to ten days To mimic the normal physiological response, adequate cortisone must be available when anaesthesia begins and the rate of availability must not only rise steeply as operation proceeds but remain high during the early phase of recovery As recovery progresses the demand diminishes and normal maintenance levels only will be required

For this purpose the standard preparations available are (1) suspension of cortisone acetate for intramuscular use (2) a solution of hydrocortisone for intravenous use and (3) tablets of cortisone acetate and hydrocortisone acetate for oral administration

Preparations of hydrocortisone acetate are unsuitable for parenteral substitution therapy the absorption being uncertain and irregular They are, of course frequently used for local infiltration for which purpose they have great usefulness

Production and maintenance of cortisone level

The absorption of cortisone acetate after oral administration is rapid and reliable but it is difficult to produce constancy of the blood level by this means The rapid absorption and utilization eventually imply fluctuation unless un necessarily large doses are given at frequent intervals which can only result in abnormally high levels if the corresponding lowering by utilization is not to produce any undue fall With simple maintenance therapy this factor is relatively unimportant, but immediately assumes great significance when great demands are

being made on the cortisone supply Excellent examples of this difficulty can be seen when patients with adrenal or pituitary gland insufficiency have to be managed with complicating disease, particularly infection It is even better demonstrated in congenital adrenal hyperplasia, for one can follow easily the demand for cortisone quantitatively In this condition there is an inborn error which prevents the elaboration of normal adrenal cortical secretion Such absence produces a chronic state of hypoadrenalism a gross excess of corticotrophin output, and hyperplasia of the adrenal with the production of large amounts of pathological adrenal steroids which are excreted in the urine Adequate main tenance with cortisone can prevent this pathological activity (Wilkins and his colleagues 1950 1952) It is however, remarkable how quickly escape from control can occur Immediately the level of cortisone declines corticotrophin is released and the adrenal gland is stimulated, in this circumstance, to pathological activity It is from this disease that we have learned how constant the cortisone level is and must be kept We discussed too how difficult this is to achieve with oral therapy, and we have learned only too well how rapid is the need for increased supplies of cortisone in the presence of stress Even a minor infection can break the control within a few hours, and more severe stress results in gross and often fatal adrenal insufficiency unless the increased demand is urgently met It has shown also how important it is to anticipate this demand for if the shock or crisis is allowed to develop fully the changes may easily become irreversible It is now well known that such patients if exposed to surgical intervention without adequate replacement seldom survive passing rapidly into a condition of shock from which they usually die within twenty four hours an example of the shock phase with no corresponding counter shock although the adrenal stimuli may be enormous Anticipation and prevention is the only safe course

Scheme of management

Oral therapy pre operatively can only be an adjuvant and reliance must be placed on the parenteral route Cortisone acetate should be given intramuscularly It is not absorbed quickly and to ensure an adequate level at the initiation of surgical operations injections must be given at least 24 hours before Not less than 100 milligrams should be injected intramuscularly and this dose should be repeated 12 hours before operation At the beginning of the operation hydro cortisone should be given intravenously diluted in saline or glucose solution so that 50 milligrams shall be given during the operative procedure and 50 milligrams over the 6–8 hours post operatively For 48 hours after operation cortisone acetate should be given intramuscularly every 12 hours in doses of 100 milligrams The dose can then be reduced to 50 milligrams for the next two days It should then be possible to begin oral maintenance treatment with 25 milligrams by mouth every 8 hours reducing to 12 hourly administration by the seventh or eighth day Should any complications arise they should be treated as for the initial stress the dose and route of cortisone administration being commensurate with the severity of the stress The final maintenance dose usually is between 25 and 50 milligrams a day of either cortisone acetate or hydrocortisone acetate by mouth

This scheme of management is applicable whenever it is suspected that an adequate pituitary or adrenal response to stress may not occur In conditions of

pituitary or adrenal ablation it is, of course, obligatory it is equally obligatory when there is known disease of either of these endocrine glands In other circumstances the decision is much more difficult and here the need for a test of the responsiveness is urgently required In addition the decision may have to be made in conditions of emergency, and as has been mentioned earlier it may be difficult to repair a wrong decision, for the resulting collapse may easily prove irreversible It is easy, perhaps, to overstress the frequency of the danger and it is surprising how well the adrenal gland may respond in what may appear to be adverse circumstances Caution, however, is required, particularly in circumstances when prolonged and repeated stress precedes the present circumstance This is particularly noticeable after prolonged intoxication from infection after prolonged inanition, and in circumstances which interfere with normal intestinal function The difficulties of the operative and post operative course of patients with chronic ulcerative colitis with chronic intestinal obstruction, and with gastro colic fistula *need not be emphasized here for the difficulties are so well known It is in these* circumstances that care in maintaining an adequate cover to prevent irreversible shock can show its greatest value In an emergency intravenous hydrocortisone is available and, if there be time, pre operative cortisone, as previously described should be used It is not to be thought that in these and related conditions every operation should be covered in this way In many cases it is unnecessary but when the issue is in doubt the cover may prove of inestimable value In the absence of specific criteria, the decision calls for the highest degree of professional skill and judgement If, after a critical review, there be present any evidence of hypo adrenalism, then the decision is easy substitution is required If there be gross electrolyte disturbance particularly sodium depletion, substitution is beneficial If there be obvious inanition or malnutrition substitution is advantageous The rest lies at present in the bewildering paths of experience, fallacious though this may be at times and clinical judgement, which is notoriously difficult

It is fortunate that unless the substitution used is overlavish the risks are small In serious stress the demand for cortisone is so high that to prevent the natural reaction is almost impossible It is in prolonged over substitution that the risks are great It is therefore better and safer to err on the side of caution rather than to risk adrenal failure, bearing in mind that some conditions may be aggravated even by short term administration

THE CONTRA INDICATIONS TO CORTISONE THERAPY

Tuberculosis

Active tuberculosis can be aggravated by the administration of either cortisone or corticotrophin The disease may spread and even disseminate The need for substitution in the presence of adrenal insufficiency still remains, and indeed such substitution can be only beneficial In some circumstances, also, high doses are used with benefit when the infection is controlled by antibiotics and chemo therapy It is, however in the uncontrolled or unrecognized lesions that the main danger lies, for the risk of spread of disease post operatively even without exogenous cortisone is well recognized

Peptic ulcer

The same sequence is essentially true with peptic ulcer There is no doubt that the administration of cortisone can have a deleterious effect on peptic ulceration for haemorrhage and perforation have frequently occurred (Davis and Zellar 1952) It is probable, too that fresh ulceration may be produced Here again it is not physiological substitution with cortisone which is harmful, but administration in high doses The frequent exacerbation of peptic ulcer by surgical or traumatic stress presumably indicates a similar effect from endogenous cortisone Peptic ulceration does not therefore preclude the use of cortisone if indicated for the operative and post operative periods but indicates the necessity for caution in dosage

Diabetes mellitus

Diabetes mellitus is aggravated by the administration of cortisone Provided this is recognized the diabetes mellitus can still be easily controlled by insulin Here the risk lies in non recognition of the diabetes mellitus or failure to take precautionary measures to prevent the disease becoming uncontrolled

Congestive heart failure, arterial hypertension

In the presence of congestive heart failure, cortisone should not be used unless it be considered life saving Even the short term administration of comparatively large doses will inevitably result in an increase of the water and salt retention and deterioration in the heart failure Cortisone is best avoided also in the presence of arterial hypertension for sometimes a marked increase in the blood pressure may occur

Pregnancy

It is often stated that cortisone should not be used during pregnancy It is difficult to understand that harmful effects could occur in human pregnancy, since the endogenous production of corticoids at this time is enormous and it would be difficult to make much impression on this quantity by exogenous cortisone It is however possible that in early pregnancy it might be hazardous and there is some evidence that foetal abnormalities may occur In early pregnancy therefore cortisone should be avoided unless life saving After the sixth month the evidence of harm is not forthcoming (De Costa and Abelman 1952)

Adrenal gland dysfunction

Clearly in abnormalities of the adrenal which result in excessive corticoid production such as Cushing s syndrome it is unnecessary to consider the use of cortisone unless surgical treatment for the disease is contemplated Substitution for the adrenal response is required as previously described but in these as in other circumstances of prolonged endogenous over production of cortisone it is essential to remember that account must be taken of the normal level of cortisone to which the patients have been subjected The usual scheme of dose range is based on a true normal basal level The increase in blood level could approximate to the normal level in Cushing s disease If the appropriate substitution dose be not enhanced manyfold the adrenal removal would result in a gross fall of cortisone

level even though the substitution under normal circumstances would produce a rise adequate for the stress Substitution in these circumstances should be additional to the calculated daily output of the disease in terms of cortisone if apparent adrenal insufficiency is to be avoided

Psychotic episodes as side-effects to cortisone

It is not rare for patients receiving cortisone to develop a psychotic episode Although account must be taken of this in long term treatment the short term use for covering acute stress is unlikely to increase the hazard materially above the risk of such an episode following the natural response, a phenomenon well recognized in the post operative period

Provided that the substitution with cortisone is short and that if therapy for any reason is continued only maintenance doses are given, other untoward effects are unlikely Such substitution and maintenance should not exceed the normal physiological levels If high unphysiological doses be prolonged then the risk of inducing Cushing s syndrome becomes considerable If this phase be reached considerable difficulty may present itself for the signs of intercurrent infection may be masked and delay in healing may occur

THE INFLUENCE OF PREVIOUS TREATMENT WITH CORTISONE

Many reports have substantiated the fact that, following prolonged administration of cortisone there may develop a greater or less degree of functional adrenal cortical atrophy (Engelman and his colleagues 1953) Once this has been induced it may not recover spontaneously for months, or even possibly years (Fraser Preuss and Bigford 1951) In some patients the atrophy appears resistant to exogenous corticotrophin This has led many workers to intersperse courses of *corticotrophin during long continued cortisone treatment Whether this is* uniformly successful is unknown but even after treatment with corticotrophin alone functional atrophy has followed although much less frequently than in the case with cortisone

These findings together with experimental data have led to endeavours to induce cortical atrophy producing a medical adrenalectomy This has been used in some conditions of adrenal overactivity particularly in the acquired adreno genital syndrome but more frequently in the treatment of advanced cancer of the breast and prostate both for therapeutic use and also to render easier the operation of adrenalectomy Exposure of the adrenals after massive cortisone administration has proved a valuable aid to our knowledge Although in some cases it has proved possible greatly to reduce the size and vascularity of the glands in the majority on the same dose little if any effect was seen Moreover the degree of Cushing s syndrome produced is also variable and sometimes only minor effects are observed, even with high doses It is thought that this represents an example of the variable utilization of cortisone and if as in many such cases continuing somatic stress produces a greatly increased demand for cortisone it would be more difficult and at times impossible to saturate continuously this demand by exogenous cortisone This would explain the ultimate phase of exhaustion in such

patients when the adaptation energy has come to an end It is interesting to note that many such patients show a progressive decline in 17 ketosteroid excretion similar to the decline obtained with repeated surgical trauma It is well known, too that in such advanced cases which have to be subjected to surgical intervention recovery from the trauma is dubious and the counter shock phenomena are lacking

It is not known how long treatment with cortisone must be continued or what is the critical over all dosage required to cause adrenal atrophy Therefore any previous treatment must be viewed with suspicion if surgical intervention is contemplated Unless time allows adequate investigation of adrenal function treatment with cortisone should be restarted before operation or hydrocortisone given during operation and treatment continued during the post operative course It is only in this way that sudden and severe adrenal failure may be prevented

REFERENCES

Albright F (1943a) Present theory of the role of the alarm reaction in convalescence *Josiah Macy Jr Foundation Conference on metabolic aspects of convalescence including bone and wound healing* 4th Meeting June 1943 New York City

— (1943b) The relation of the adrenal gland to damage Cushing s syndrome and the alarm reaction *Ibid* 3rd Meeting March 1943 New York City

Cuthbertson D F (1932) Observations on the disturbance of metabolism produced by injury to the limbs *Quart J Med* 1 233

Davis T A and Zellar M (1952) Multiple peptic ulcers with massive haemorrhage during oral cortisone therapy report of a case *J Amer med Ass* 150 31

De Costa E J and Abelman M A (1952) Cortisone and pregnancy an experimental and clinical study of the effects of cortisone on gestation *Amer J Obstet Gynec* 64 746

Engel F L (1951) A consideration of the roles of the adrenal cortex and stress in the regulation of protein metabolism *Recent Progr Hormone Res* 6 277

— (1953) The anterior pituitary and adrenal cortex *Annu Rev Physiol* 15 397

Engelman E P Krupp M A Johnson H P Jr Welsh J E Wrenn H T and King W R (1953) Adrenocortical function during continuous long term therapy with cortisone *Arch intern Med* 91 1

Farrell G L and McCann S M (1952) Detectable amounts of adrenocorticotrophin hormone in blood following epinephrine *Endocrinology* 50 274

Fortier C (1951) Dual control of adrenocorticotrophin release *Endocrinology* 49 782

Fraser C G Preuss S F and Bigford W D (1951) Adrenal atrophy and irreversible shock associated with cortisone therapy *J Amer med Ass* 149 1542

Hardy J D and Ravdin I S (1952) Some physiological aspects of surgical trauma *Ann Surg* 138 345

— and Cole F H (1953) The metabolic reaction to staged operations in man *Fundamental Forum* Philadelphia W B Saunders

— Richardson E M and Dohan F C (1953) The urinary excretion of corticoids and 17 ketosteroids following major operations Correlation with other aspects of metabolism *Surg Gynec Obstet* 96 1

Huggins C and Bergenstal D M (1951) Surgery of adrenals *J Amer med Ass* 147 101

— — (1952) Inhibition of human mammary and prostatic cancers by adrenalectomy *Cancer Res* 12 134

Hume D M (1953) The neuro-endocrine response to injury Present status of the problem *Ann Surg* 138 548

Ingle D J (1942) Problems related to the adrenal cortex *Endocrinology* 31 419

— (1951) Functional inter relationship of the anterior pituitary and the adrenal cortex *Ann intern Med* 35 652

Long C N H (1950) *Factors Regulating the Adrenal Cortical Secretion in Pituitary Adrenal Function* Washington D C American Association for the Advancement of Science

Luft R and Olivecrona H (1953) Experiences with hypophysectomy in man *J Neurosurg* 10 301

— — (1955) Hypophysectomy in man experiences in metastatic cancer of the breast *Cancer* 8 261

— — (1957) Hypophysectomy in the management of neoplastic disease *Bull N Y Acad Med* 33 5

— — and Sjogren B (1952) Hypophysectomy in man *Nord med* 47 351

— — Ikkof D Nilsson L B and Junggren H (1956) Hypophysectomy in the treatment of malignant tumours *Amer J Med* 21 728

Moore F D and Ball M R (1952) *The Metabolic Response to Surgery* Springfield Thomas

Pearson O H (1956) Adrenalectomy and hypophysectomy in the treatment of advanced cancer *Advanc internal Med* 8 205

— Ray B S, Harrold C C West C D Li M C MacLean J P and Lipsett M B (1955) Hypophysectomy in the treatment of advanced cancer *Trans Ass Amer Physcns* 68 101

— — Harrold C C West C D Li M C MacLean J P and Lipsett M B (1956) Hypophysectomy in treatment of advanced cancer *J Amer med Ass* 161 17

— Whitmore W F West C D Farrow J H and Randall H T (1953) Clinical and metabolic studies of bilateral adrenalectomy for advanced cancer in man *Surgery* 34 543

— Lipsett M B and Li M C (1956) Medical management of adrenalectomy and hypophysectomy *Arch intern Med* 98 634

Ray B S and Pearson O H (1956) Hypophysectomy in the treatment of advanced cancer of breast *Ann Surg* 144 394

Recant, L Hume D M Forsham P H and Thorn G W (1950) Studies on the effect of epinephrine on the pituitary adrenocortical system *J clin Endocrin* 10 187

Selye H (1937) Studies on adaptation *Endocrinology* 21 169

— (1944) General adaptation syndrome *Josiah Macy Jr Foundation Conference on metabolic aspects of convalescence including bone and wound healing* 8th Meeting October 1944 New York City

— (1946) The general adaptation syndrome and the diseases of adaptation *J clin Endocrin* 6 117

Sprague R G Power M H Mason H L Albert A Mathieson D R Hench P S Kendall E C Slocumb C H and Polley H F (1950) Observations on the physiologic effects of cortisone and ACTH in man *Arch intern Med* 85 199

Sydnor K L Kelley V C Raile R B Ely B S and Sayers G (1953) Blood adrenocorticotrophin in children with congenital adrenal hyperplasia *Proc Soc exp Biol N Y* 82 695

Thorn G W Forsham P H Prunty F T G and Hills A G (1948) Test for adrenal cortical insufficiency response to pituitary adrenocorticotrophin *J Amer med Ass* 137 1005

Wilkins L Lewis R A Klein R and Rosenberg E (1950) The suppression of androgen secretion by cortisone in a case of congenital adrenal hyperplasia *Johns Hopk Hosp Bull* 86 249

— Gardner L I Crigler J F Jr Silverman S H and Migeon C J (1952) Further studies on the treatment of congenital adrenal hyperplasia with cortisone I Comparison of oral and intramuscular administration of cortisone with a note on the suppressive action of compounds F and B on the adrenal *J clin Endocrin* 12 257

Wolfson W Q (1953) Inadequacy of epinephrine as an activator of the pituitary adrenal system *J clin Endocrin* 13 125

CHAPTER 14

ANAESTHESIA AND THE AUTONOMIC NERVOUS SYSTEM INDUCED HYPOTENSION

J B WYMAN

TECHNIQUES TO PRODUCE HYPOTENSION

IT IS NOT intended here to discuss the techniques of hypotension in detail but only to point to new knowledge and to attempt some assessment of the value of this procedure as it appears at the time of writing

Although hypotension can be induced by several methods there are in fact only two events that cause a diminution in bleeding at operation These are (1) vasoconstriction which prevents the vessels from bleeding and (2) vasodilatation and a resulting pooling of blood in dependent parts of the body

The technique of arteriotomy as introduced by Gardner (1946) and used in neurosurgery by both Bisland (1951) and Mortimer (1951) is in itself an elaborate surgical procedure and with improvements in other hypotensive techniques is falling into disuse It is interesting as Gillies (1952) points out that this principle was first used by Harvey Cushing who would allow patients to bleed during neurosurgical procedures because he found that this lowered the tension of the brain and allowed tumours to be handled with greater safety

The other approach is to achieve hypotension by the production of vasodilatation Vasodilatation can be brought about by general anaesthesia by spinal and epidural anaesthesia or by the intravenous injection of drugs which block trans mission in the sympathetic ganglia It may be seen from Table I (adapted from Gillies 1952) that except when the agent is chloroform the pharmacological changes induced by the usual methods of maintaining light anaesthesia are conducive to haemorrhage

The vasodilatation which is mainly of the superficial vessels during light anaesthesia becomes generalized as the anaesthesia deepens the blood pressure and the cardiac output fall and a dry surgical field results Thus any general anaesthetic can produce hypotension but generally speaking only in the deeper stages which are not justified To produce working conditions comparable to deep anaesthesia with the advantages of submitting the patients to the lighter planes only necessitates the use of sympathetic blockade either by spinal or epidural anaesthesia or by the use of ganglion blocking agents

Spinal and epidural block

Spinal and epidural block have disadvantages Not only is the patient exposed to

TABLE I

PHARMACOLOGICAL CHANGES INDUCED BY ANAESTHETIC AGENTS

Ether (light)	(1) Superficial vasodilatation (2) Increased cardiac output (3) Pulse pressure raised (Systolic rises—diastolic unchanged)	Increased haemorrhage
Cyclopropane (light)	(1) Arterial pressure normal (2) Cardiac output increased (3) Vasodilatation (4) Pulse pressure raised (Systolic normal—diastolic falls)	Increased haemorrhage
Intravenous barbiturates	(1) Vasodilatation (2) Transient fall in blood pressure	Increased haemorrhage
Chloroform	*(1) Vasodilatation* (2) Depression of vasomotor centre (3) Cardiac output decreased (4) Pulse pressure lowered	*Dry field*

whatever hazards there are involved in the production of hypotension but these techniques carry their own risks Although most of the complications of spinal anaesthesia can be avoided by a careful and scrupulously aseptic technique others for example headache and possibly some neurological sequelae are at present beyond the control of the anaesthetist and can cause a patient severe post operative stress A further disadvantage is that it is impossible to control the extent and the duration of the hypotension

The introduction of the analgesic drugs into the epidural space obviates some of the disadvantages of spinal anaesthesia However the nature of the epidural space makes it difficult to achieve the gradual dilution of the anaesthetic drug at the higher levels in order to produce differential block of the sympathetic fibres The use of more dilute solutions so that only the sympathetic fibres are affected necessi*tates the use of supplementary general anaesthesia thus making the technique more* elaborate and clumsy

Ganglion block

There remains ganglionic blockade which has proved the most satisfactory method The drugs which have been used to block the autonomic ganglia during anaesthesia are the lower members of the methonium series (pentamethonium and hexamethonium) trimetaphan (Arfonad) and pentolinium tartrate (Ansolysen) These drugs all cause a fall in blood pressure and clinically they are indistinguish able except as regards the duration of their action Pentolinium appears to have the longest action followed by the methonium compounds trimetaphan of course is the shortest acting Obviously the duration of effect will depend on the dosage and therefore trimetaphan is best used in a dilute solution (1 milligram per millilitre) given as an intravenous drip when its effect is almost evanescent When ever possible it seems preferable to use drugs which are not only specific in action but also of short duration as by this means the greater control must be achieved Hence the administration of trimetaphan by intravenous drip is an improvement

over the former technique of intermittent injection of larger doses say 25 milligrams (Scurr and Wyman 1954) Using the method of continuous infusion it is possible to obtain a finely graded control of the falling blood pressure and a return to normal tension when the operation is completed In elderly patients it is easier to control the hypotension if the solution is diluted to 0 5 milligram of trimetaphan per millilitre Overdosage is not dangerous—it merely extends the time taken for the pressure to return to normal Once the ganglia are blocked any further action of the drug does not increase the extent of the hypotension It must be remembered, however, that the general anaesthesia plays a part in the hypotension and full restoration of the blood pressure may not occur until the anaesthetic has been discontinued Obviously the deeper the anaesthetic the more likely is this to occur The evanescent effect of trimetaphan has removed all post operative worries due to prolonged hypotension and although it is more difficult to use, the control achieved is amply worth the trouble

Trophenium (phenacyl homatropinium chloride) was first introduced as an intravenous hypotensive agent by Robertson, Gillies and Spencer (1957)

Pharmacologically it is said to differ from trimetaphan in that it is a pure sympathetic ganglionic blocking agent It was found to be much less active than trimetaphan as a histamine liberator and has negligible atropine like side reactions Clinically it is indistinguishable from trimetaphan the blood pressure returning to normal in about the same time In the author s series there is a suspicion that the number of failures to produce adequate hypotension is greater than with trimetaphan Nevertheless, the drug is worthy of extended trial

The use of posture

Posture may be used to serve two purposes (1) to help lower the blood pressure in difficult subjects and (2) to help drain the site of operation

Extremes of posture are both unnecessary and dangerous, and apart from a few degrees of the anti Trendelenburg position in young resistant patients it is rarely necessary to depart from the conventional position that the operation demands It is in the skin that it is difficult to get a really dry field and if this is important as in plastic surgery then it is advisable to drain the area for as long a time as possible before the operation commences The steep head up position can be very dangerous except in the young and fit as the pooling in the legs becomes excessive and the venous return to the heart seriously reduced The respirations have been seen to stop in a steep head up position only to return spontaneously when the table was levelled indicating a diminished blood supply to the medulla In addition quite large veins have been seen to start to bleed when the table has been levelled and, if the pressure is still low it is advisable to do this deliberately when the wound is about to be closed Finally, in patients sensitive to this technique an excessive drop in blood pressure may be immediately corrected by placing the patient in one or two degrees of Trendelenburg position

The anaesthesia

There is no particular merit in the type of general anaesthesia employed but only in the quality of the anaesthesia used The patient must be quite settled before hypotension is induced There must be no coughing gagging laryngeal spasm or

indeed, anything that may produce even temporary asphyxia The danger of inducing hypotension in a patient not adequately oxygenated cannot be sufficiently stressed The effect of the ensuing hypotension on an anoxic myocardium is very dangerous and the attempt to quieten such a patient with further anaesthetic may prove fatal If there is a serious asphyxial episode during induction it is much wiser to abandon the technique *The author strongly recommends endotracheal* anaesthesia in all cases of induced hypotension

CHANGES IN HOMEOSTASIS ASSOCIATED WITH HYPOTENSIVE TECHNIQUE

The problems of this technique may be divided into two groups (1) the integrity of the blood supply to the major organs—the heart, brain liver and kidneys and (2) the precipitation of vascular accidents—reactionary haemorrhage pulmonary embolism and other embolic hazards

The heart

An unchanged or even slightly increased cardiac output with decreased peripheral resistance means decreased cardiac work and therefore increased tolerance to *diminished coronary flow That the coronary flow is diminished is indicated* by the fall in mean blood pressure—the mean blood pressure is an indication of the filling pressure for the coronary arteries

The critical test is whether the coronary flow such as it is during the hypotension suffices for cardiac muscle working at a lower load

In the early work with this technique it was found that the electrocardiographic readings showed no changes either during the period of hypotension or post operatively but a sufficient number of chest leads had not been examined

In thirty unselected cases electrocardiographic readings examined by the author showed changes in all but two The most frequent change was a lowering of the T wave or sometimes a flattening of that wave in one or more of the chest leads This change was reversible in all cases but on occasions it persisted for a few days Rollason and Cunning (1956) have confirmed that no permanent changes occur

Earlier, the author (Wyman 1953) reported two cases of cardiac arrest during hypotension pointing out that the reason was inexperience and allowance of the technique to be used after severe asphyxia during the induction This has never happened since and from a growing experience of using this technique on patients with impaired hearts it is considered that induced hypotension does not affect the myocardium

The brain and the cerebral circulation

In the author s series there have been two cases of cerebral thrombosis both in patients with histories of a previous cerebral catastrophe This may be a contra indication to the technique but many such cases have been reported without the use of hypotension There has also been one case of cerebral damage due to hypo tension following severe anoxia Again this was early on in the series and it does not require hypotension to produce this state (Hunter, 1950, Courville, 1936 1938)

These castastrophes have been due to errors in technique and since correction they have not recurred

It has been shown (Enderby 1954) that when the body is tilted gravity induces a gradient in arterial pressure (30 millimetres of mercury for every 15 inches vertical height from heart level) Thus for neurological operations in which the head up position is used it has been found necessary only to lower the blood pressure to 90 millimetres of mercury to produce excellent working conditions There has been a great deal of work done on the cerebral circulation (Van Bergen and his colleagues, 1954 Hughes 1954) but it is not conclusive Electroencephalograms indicate that all cortical activity ceases when the systolic pressure falls to 55 millimetres of mercury (Van Bergen and his colleagues, 1954 Bromage 1952a Schallek and Walz 1954) Also some alteration in cerebral function has been shown by the flicker fusion test of Berg (Nilson 1953) Burrows and his colleagues (1956) suggest that hypothermia renders hypotension safer during neurosurgery

The kidneys and liver

There have been no cases of liver or kidney damage following this procedure except in one patient who was found to have Ellis Type I kidneys The kidneys were small, and it is believed that surgery was invariably fatal to these patients when this disease was more common Hepatic and renal blood flows may not be greatly disturbed during hypotension although naked eye changes have been observed (Miles and his colleagues 1952 de Wardener 1955 Evans and Enderby 1952, Bromage 1952b)

Blood loss and reactionary haemorrhage

The fear that this method of anaesthesia would lead to frequent reactionary haemorrhages proved unfounded The very fact that the fall in blood pressure is due

TABLE II

AVERAGE BLOOD LOSS IN TYPICAL OPERATIONS

Operation	*Average Blood Loss (millilitres)*	
	With hypotension	*Without hypotension*
Thyroidectomy	26	247
Radical mastectomy	32	690
Prostatectomy	30	551
Thoracotomy	160	1158
Pelvic evisceration	157	1500

to vasodilatation means that cut vessels do bleed As the bleeding is not profuse and as there is no capillary oozing the bleeding points can easily be seen and stopped Thus it is impossible with this technique to get a dry field as good as that obtained with adrenaline infiltration but considerable attenuation of the blood loss can be obtained as shown in Table II

It is obvious that the success of controlled hypotension depends a great deal

upon the efficiency of the surgeon and his assistants in picking up the bleeding points, but with their help the blood loss during major operations can be reduced to a minimum When these patients go back to the ward and their blood pressure is again normal they will lose blood from the circulation post operatively, as do patients anaesthetized with conventional forms of anaesthesia who have had a wide raw area exposed Thus after operations such as pelvic eviscerations abdomino perineal resections of the rectum and hindquarter amputations, a pint of blood should be given as a routine It is in these very major procedures that the true worth of the hypotensive technique is seen

Pulmonary embolism and coronary thrombosis

There has not been any increase in the incidence of pulmonary embolism in these cases, nor in the incidence of post operative coronary thrombosis

TABLE III

ESTIMATION OF CIRCULATION TIME IN NORMAL PATIENTS

Route right arm to left leg	
Time in seconds (9 cases)	12 15 51 26 21 12 14 60 43
Mean value	30.6 seconds
Standard deviation	6.2 seconds

The circulation time and other cardiovascular changes

Radioactive sodium has been used in an attempt to measure the circulation time in normal, anaesthetized and hypotensive patients A wide variation was found in unanaesthetized patients (Table III)

The circulation times of the same patients under ordinary anaesthesia always showed a slowing (Table IV)

TABLE IV

ESTIMATION OF CIRCULATION TIME IN NORMAL PATIENTS UNDER ORDINARY ANAESTHESIA

Case No	*In ward Time in seconds*	*Under anaesthesia Time in seconds*
2	22	32
3	21	28
4	10	16
5	19	40

When the times were compared with patients in whom hypotension had been induced there was comparatively little slowing again (Table V)

If however the circulation time from foot to neck was made in cases under hypotension there was always a slowing

TABLE V

ESTIMATION OF CIRCULATION TIME IN HYPOTENSIVE PATIENTS

Case No	*In ward*		*Under anaesthesia with hypotension*	
	Time in seconds	*Blood pressure*	*Time in seconds*	*Blood pressure*
1	23	105/80	27	60/50
6	25	128/85	20	60/40
2	22	220/160	26	40/35

These cases are too few in number to draw positive conclusions but they do suggest that there is not a marked slowing of the circulation time, even when the blood pressure is reduced considerably

Direct observation of the capillaries through a skin microscope revealed no obvious disturbance in the rate of flow of corpuscles

The clotting and bleeding times are unaltered Haemodilution occurs when the blood pressure falls and it appears to vary with the pressure

The intra-ocular pressure has been measured and this too falls with the blood pressure One case of amaurosis with partial improvement has been reported (Goldsmith and Hewer 1952) but as this was thought to be due to spasm of the retinal artery it is difficult to implicate a technique that causes vasodilatation Direct observations of the retina reveal no changes during hypotension

The blood pressure

By means of an electromanometer the intra arterial pressures have been measured directly in the aorta renal and femoral vessels and the variations in pressure have been found to correspond directly with those recorded with the brachial stethoscope The pressure in the pulmonary artery has also been measured showing a fall from 30/12 to 12/8 millimetres of mercury

Adrenocortical response

Thorn s test showed that there was a prompt cortical response and the eosinophils disappeared within a short time of operation

CONDITION OF THE PATIENT UNDER HYPOTENSION

Once the idea is accepted that a patient can exist in a state of extreme hypotension without coming to any harm there is less cause to worry about the condition of the patient than with any other form of anaesthesia The patients are warm dry and of good colour If the posture of the patient causes the face to appear pale due to drainage a gentle rubbing of the ears or face will immediately produce a brisk capillary response and the parts so rubbed will immediately flush The pupils are usually widely dilated this being one of the earliest signs that the drug is acting This sign however may be delayed in aged patients The respiration is unimpaired

and the pulse steady Controlled respiration lowers the blood pressure about 20 millimetres of mercury and this is evidenced frequently by the sudden rise in blood pressure when automatic respiration is restored

The superficial temporal and carotid arteries are easily palpable even when the pressure is low once experience in feeling pulses at such pressures has been ap preciated

The general condition of the patient remains unaltered and unaffected irrespective of the extent of the trauma The conservation of blood during the operation is an important factor and it is interesting to see what happens to a patient when a large quantity of blood is lost during the state of hypotension This occurred in three patients and in each instance it was due to damage to a large vein buried in a mass of malignant tissue The lost blood was immediately replaced and at no time did the patient s condition give rise to anxiety It appears that sudden heavy blood loss during hypotension with this technique may not be the overwhelming disaster that has been anticipated

POST-OPERATIVE CARE

The evanescent action of trimetaphan has eliminated a great deal of the post operative worries that accompanied the use of longer acting drugs If the blood pressure has not returned to normal at the end of the operation, the patient must be returned to the ward in the head down position and must remain so until this occurs The hypotension does not delay the return of consciousness and the patients are quite comfortable even if the pressure is still low Vasopressor drugs such as adrenaline noradrenaline and methylamphetamine rapidly restore the normal pressures but as these are not physiological antidotes care must be taken that the drop in pressure does not recur once their effect has worn off The methonium compounds are excreted unchanged in the urine and 0 5–1 litre of 5 per cent dextrose helps to eliminate the drug more effectively than do the vasopressors

CONTRA-INDICATIONS

Inexperienced personnel

This is not a technique for the trainee or occasional anaesthetist as the penalties are high for infringements of basic anaesthetic principles

Non-cooperative surgeon

The cooperation of the surgeon is essential as not only must he be aware of what is happening but he must understand the implications All bleeding points however small must be ligated or sealed with the diathermy that is cautery otherwise whatever advantage is obtained during the operation will be lost in the post operative phase

Severe cardiac disease

The present knowledge of using this technique in cardiac patients is limited and it has been thought unwise to subject an impaired heart to sudden fluctuations of

coronary pressures In cases of coarctation of the aorta the technique has been of great assistance, although Vale (1956) attributes post operative haemorrhage in one patient to the subsequent rise in blood pressure after the chest had been closed

Circulatory failure

This must also be considered a contra indication until proved otherwise

Severe kidney disease

Some of the drugs used to procure hypotension are excreted unchanged by the kidneys and if these are diseased the restoration of the pre operative blood pressure may be long delayed

Respiratory inefficiency

This contra indication includes severe anaemia or anoxia from any cause

Severe diabetes mellitus

The hypotension induced by hexamethonium appears to potentiate the action of insulin and hypoglycaemic coma may ensue which is masked by the hypotensive anaesthesia (Griffiths 1953)

INDICATIONS

The indications for the use of hypotension are limited to the case in which blood loss either prejudices the successful outcome of the operation or in which, although it is small in quantity, it hampers the surgeon working in a confined space The number of patients in whom it can be used will be very small but if these are correctly selected the technique will be a valuable addition to the anaesthetists armamentarium

CONCLUSION

Controlled hypotension will be of use in only a small number of problems that daily face the anaesthetist The technique complicates ordinary anaesthesia and should be undertaken only when the advantages obtained justify its use

The early pitfalls that beset the anaesthetist using this technique have been discussed and it might be thought overcome It is during this early period that the mortality figure of 1 450 suggested by Hampton and Little (1954) was obtained (equivalent to the mortality figures for muscle relaxants without anaesthesia revealed in the United States of America by Beecher and Todd, 1953) Any additional risk depends upon the skill of the anaesthetist and a proper understanding of the implications of the technique A series of fatalities has been published in which the hypotensive technique had been used, but they largely demonstrate what has already been stressed—the dangers of poor anaesthetic technique accompanying this form of anaesthesia Any deviation from the stringent rules is followed by the heaviest penalties

Many authorities disapprove of this technique and their views (Gray 1957 Davison, 1953) are worthy of great consideration, but in a widening experience this technique has in expert hands proved safe and of great benefit to the patients and surgeon

REFERENCES

Beecher H K and Todd D P (1954) *Ann Surg* 140 11
Bisland W L (1951) *Anaesthesia* 6 20
Bromage P R (1952a) *Proc R Soc Med* 46 919
— (1952b) *Lancet* 2 10
Burrows M McC Dundee J W Francis I L Lipton S and Sedzimir C B (1956) *Anaesthesia* 11 4
Courville C B (1936) *Medicine Baltimore* 15 129
— (1938) *Ann Surg* 107 371
Davison M H A (1953) *Anaesthesia* 8 255
de Wardener H E (1955) *Anaesthesia* 10 18
Enderby G E H (1954) *Lancet* 1 185
Evans B and Enderby G E H (1952) *Lancet* 1 1045
Gardner W J (1946) *J Amer med Ass* 132 572
Gillies J (1952) In *British Surgical Practice* Ed by Sir J Paterson Ross and Sir E Rock Carling London Butterworths
Goldsmith A J B and Hewer C L (1952) *Brit med J* 2 759
Gray T C (1957) *Lancet* 1 383
Griffiths J A (1953) *Quart J Med* 22 405
Hampton L J and Little D M (1953) *Lancet* 1 1299
Hughes G (1954) *Lancet* 1 311
Hunter A R (1950) *Lancet* 1 251
Miles B E de Wardener H E Churchill Davison H C and Wylie W D (1952) *Clin Sci* 11 73
Mortimer P L F (1951) *Anaesthesia* 6 25
Nilson E (1953) *Brit J Anaesth* 25 24
Robertson J D Gillies J and Spencer K E V (1957) *Brit J Anaesth* 29 342
Rollason W N and Cunning A R R (1956) *Anaesthesia* 11 319
Schallek W and Walz D (1954) *Anesthesiology* 15 673
Scurr C F and Wyman J B (1954) *Lancet* 1 338
Vale R J (1956) *Anaesthesia* 11 232
Van Bergen F H Buckley J J French L A Dobkin A B and Brown I A (1954) *Anesthesiology* 15 507
Wyman J B (1953) *Proc R Soc Med* 46 605

CHAPTER 15

ANAESTHETIC FATALITIES

H J V MORTON

IT HAS been said of anaesthetic drugs that they are one of the wonders of the modern world But this is a layman s view and it is unlikely that anaesthetists ever regard them in this way An anaesthetist is more likely to have his mind on their side effects their shortcomings and the complications which they can produce One complication is death

In recent years great changes have taken place in anaesthetic practice Has there also been a change in the frequency of anaesthetic deaths? How many deaths are still due to anaesthesia? Such opening questions cannot be answered with certainty though an indication of the size of the problem may be found in the Ministry of Health Report for 1954 Here it is recorded that the number of deaths *under* anaesthesia in England and Wales has been declining year by year since 1938 (Fig 25) By 1954 there had been a reduction by over one third to 562 the latter figure representing about 1 1,000 of all deaths occurring in the population It is noteworthy that this reduction has occurred during a period of steady increase in the numbers of anaesthetics given In some hospitals these have more than doubled in the last ten years (Dawkins 1956)

The figures quoted refer to deaths *under or in association with anaesthesia* They do not represent the number of deaths *due* to anaesthesia Case details when available often show that anaesthesia receives mention on a coroner s certificate when in fact it was only incidental to the fatality On other occasions anaesthesia may escape mention although it had a causal relationship to the fatal result These discrepancies are largely explained by the many ways in which the administration of an anaesthetic may bring about death without leaving changes demonstrable *post mortem*

Beecher and Todd (1954) analysed the results of over 500 000 anaesthesias given during a 5 year period in 10 university hospitals in the United States of America They arrived at a case mortality for anaesthesia of 1 1 560 This may represent an incidence of death associated with anaesthesia of 3 29 per 100 000 of the population of that country They made the interesting comparison that more than twice as many citizens out of the total population of the country die from anaesthesia as die from poliomyelitis

REFERENCES

Beecher H K and Todd D P (1954) *Ann Surg* 140 11
Bisland W L (1951) *Anaesthesia* 6 20
Bromage P R (1952a) *Proc R Soc Med* 46 919
— (1952b) *Lancet* 2 10
Burrows M McC, Dundee J W Francis I L Lipton S and Sedzimir C B (1956) *Anaesthesia* 11 4
Courville C B (1936) *Medicine Baltimore* 15 129
— (1938) *Ann Surg* 107 371
Davison M H A (1953) *Anaesthesia* 8 255
de Wardener H E (1955) *Anaesthesia* 10 18
Enderby G E H (1954) *Lancet* 1 185
Evans B and Enderby G E H (1952) *Lancet* 1 1045
Gardner W J (1946) *J Amer med Ass* 132 572
Gillies J (1952) In *British Surgical Practice* Ed by Sir J Paterson Ross and Sir E Rock Carling London Butterworths
Goldsmith A J B and Hewer C L (1952) *Brit med J* 2 759
Gray T C (1957) *Lancet* 1 383
Griffiths J A (1953) *Quart J Med* 22 405
Hampton L J and Little D M (1953) *Lancet* 1 1299
Hughes G (1954) *Lancet* 1 311
Hunter A R (1950) *Lancet* 1 251
Miles B E de Wardener H E Churchill Davison H C and Wylie W D (1952) *Clin Sci* 11 73
Mortimer P L F (1951) *Anaesthesia* 6 25
Nilson E (1953) *Brit J Anaesth* 25 24
Robertson J D Gillies J and Spencer K E V (1957) *Brit J Anaesth* 29 342
Rollason W N and Cunning A R R (1956) *Anaesthesia* 11 319
Schallek W and Walz D (1954) *Anesthesiology* 15 673
Scurr C F and Wyman J B (1954) *Lancet* 1 338
Vale R J (1956) *Anaesthesia* 11 232
Van Bergen F H Buckley J J French L A Dobkin A B and Brown I A (1954) *Anesthesiology* 15 507
Wyman J B (1953) *Proc R Soc Med* 46 605

to draw inferences from his data was to run the risk of serious error, and that these figures cannot be accepted as representing the true relative death rates'

The phrase true relative death rates demands our closest attention It implies that the side effects of drugs may achieve fatal significance, and that in spite of the greatest skill disaster will occasionally occur—a drug may carry an inherent toxicity

Now here is something of prime importance in anaesthesia which yet may be very difficult to establish with certainty However with respect to anaesthetic deaths in general there will be little disagreement if we postulate that their occurrence is mainly a function of three factors the skill of the administrator the condition of the patient the agent used and of these the first has overwhelming importance

Anaesthetic deaths in which there has been no error of judgement or departure from accepted practice are not common yet it is only through the collection of accounts of such cases that the inherent toxicity of drugs can be demonstrated Attempts to do this require the cooperation of many contributors Each will have brought to bear varying degrees of technical skill and observational diligence and differing criteria with respect to choice of technique and assessment of a patient s general condition To distinguish between preventable and inexplicable deaths from such data must be difficult indeed

What do we mean by skill? Skill is compounded of many parts one of which is relevant knowledge To prevent anaesthetic deaths we require knowledge not only of the mechanism through which the fatality may be brought about but of the means to counteract it When both become known deaths previously attributable to inherent toxicity become deaths due to lack of skill

A LARGE-SCALE INQUIRY

Beecher and Todd (1954) in the remarkable survey already mentioned made a detailed statistical analysis of the mortality associated with the use of the muscle relaxant drugs At no time did they claim that any specific patient had been killed by the use of these drugs but their figures are to say the least very striking In brief the death rate when curare (relaxant drugs) was used was 1 370 when not used it was 1 2 100 They stated that in most cases curare deaths were not associated with gross errors of anaesthetic management Even when such important factors as the experience of the administrators major and minor operations and patient risk were taken into account the mortality figures were still always unfavourable to curare In an analysis of the primary causes of curare deaths 63 per cent were recorded as due to respiratory failure (hypoxia) and 37 per cent to cardiovascular failure (notwithstanding artificial respiration) The point was made that death *from curare can* be other than respiratory, and it was concluded that muscle relaxants have an inherent toxicity

Beecher and Todd s work was subjected to much criticism This criticism was mainly on three grounds First the design of the investigation was not suitable for discovering the actual causes of the anaesthetic deaths Secondly circulatory collapse due to relaxant drugs in spite of the use of adequate artificial respiration was something contrary to generally *accepted clinical* and pharmacological

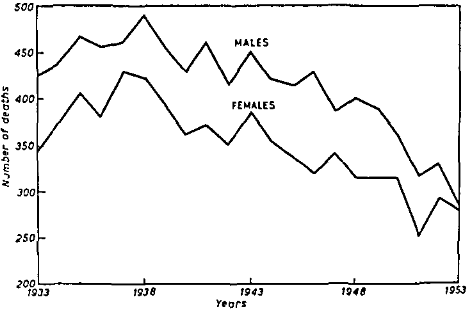

FIG 25.—Deaths under or in association with anaesthesia (England and Wales 1933–53) (*Reproduced from the Report of the Ministry of Health for 1954 by kind permission of the Controller of Her Majesty's Stationery Office*)

SEX AND AGE INCIDENCE

Where large collections of data have been studied it has been usual to find more deaths in males than in females (Edwards and his colleagues 1956, Stephenson, Reid and Hinton 1953, Brown 1950) Beecher and Todd (1954) showed that there was a real disproportion in this respect, deaths in males amounted to 58 per cent of the total whereas the proportion of males in a sample of the surgical population under study was 43 per cent They suggested that perhaps the higher incidence of heart and circulatory disease in men makes them less able to tolerate anaesthesia than women Most reviews of data also show a disproportionate number of deaths at the extremes of age particularly in the first decade

Ministry Reports record an increase in recent years in deaths under anaesthesia in the elderly We should remember however not only that the average age of the population is increasing but that advances in anaesthetic and surgical practice have made it possible to perform major surgery on cases formerly regarded as inoperable on account of their age Could deaths be related to the number of operations it might be found that there was now less risk of an elderly patient dying during a surgical operation than previously (Registrar General's Review, 1953)

INHERENT TOXICITY

The relative safety of the various agents and techniques used in anaesthesia has been a perennial subject for discussion Chloroform and ether were among the first to receive attention To quote but one example Hewitt (1912) assembled data relating to over 1 000 000 administrations The death rate with ether was 1 16 302 and with chloroform 1 3 162 But Hewitt was quick to point out that

experimenter relationship Reports of anaesthetic fatalities need to be finely detailed, and utterly factual, the *post hoc ergo propter hoc* fallacy may introduce itself in the most insidious fashion

RISKS LARGE AND SMALL

Untoward results have followed failure to appreciate the relative risks of alternative courses of action In order to avoid a very small risk a far greater one may be taken Neostigmine may or may not have been the sole cause of a very small number of deaths But many deaths in the immediate post operative period have been caused by respiratory obstruction or prolonged inadequate ventilation due to the muscular flaccidity of unreversed curarization It seems likely that the majority of such deaths would have been prevented by the use of neostigmine

The explosion risk is another example An exaggerated importance of the danger of even the briefest use of ether-air mixtures in the x ray room has led beginners to embark sometimes with fatal results on complicated non inflammable techniques with which they were not familiar (Report of the Working Party on Anaesthetic Explosions 1956)

SCEPTICISM AND TRADITION

There are some risks which are both clearly understood and universally appreciated No doctor would unhesitatingly subject a patient to general anaesthesia if he knew for certain that that patient had a full stomach In contrast there are some risks about which next to nothing is known Cases are on record where small children have suddenly and unexpectedly died during the course of trivial operations for which anaesthesia had been administered in a seemingly flawless fashion Status lymphaticus is no longer in vogue and it is customary nowadays to ascribe such deaths to vagal inhibition This explanation even if correct provides no help towards the prevention of such fatalities They are in any case so rare that the more sceptical anaesthetist may insist that they represent some unrecorded or unrecognized technical mismanagement

There are some risks that come between these two extremes and where relevant knowledge though far from complete is sufficient to enable prophylactic measures of undoubted value to be taken The risk of ' ether convulsions is an example This potentially fatal complication is sufficiently uncommon for many anaesthetists lacking first hand experience of the phenomenon and doubtless activated by scepticism to refrain from taking precautions which are both reasonable and simple Children are much more likely to develop this complication than are adults and out of a mass of previous conjecture it has emerged that there are six factors of outstanding aetiological importance namely an inborn liability sepsis atropine overheating, carbon dioxide retention and deep ether anaesthesia The last four of these are easily controlled

Apart from the deliberate use of cooling for special cases it is still customary to allow unconscious patients to become overheated This is due to the generous application of blankets and macintoshes in an atmosphere which is always hot, and often humid This practice may be due to thoughtlessness or *tradition*

opinion Thirdly, why were deaths labelled as due to respiratory failure after relaxant drugs not regarded as due to lack of skill? This last apparently justifiable criticism tended to overshadow the others Since details were not given there was *no evidence to suggest that the deaths from respiratory failure might have* been for example, instances of the rare phenomenon of neostigmine resistant curarization, subsequently described by Hunter (1956) And even then prolonged respiratory paralysis, if uncomplicated by circulatory inadequacy, has little or no sinister significance if modern equipment is available Complete recovery after even weeks of artificial respiration is nothing unusual

As to the design of the investigation, the authors themselves emphasized the value of limiting future inquiries to certain kinds of severe test situations (anaes thesia for gastric surgery, or common bile duct surgery) Although subsequent approaches to the problem have been made in this direction, none has been conducted on a scale large enough for the results to carry conviction

Concerning circulatory failure, Beecher (1954) drew attention to the importance of distinguishing between observed fact and generally accepted opinion ', and emphasized that these deaths are still infrequent enough for any given anaesthetist to have a thousand or two cases without a death attributable to curare Anaesthetic deaths in the form of cardiovascular failure following ' curare were recorded at the rate of 1 1,000 administrations which gives an indication of the size needed for any future inquiry aimed at a statistical investigation of this problem

POST HOC ERGO PROPTER HOC?

Trichloroethylene is known to be capable of causing cardiac arrhythmias of a potentially dangerous type This agent is widely used in Britain yet recorded fatalities in which it might be directly implicated are very rare Hewer (1956) reports 40 000 consecutive administrations with three fatalities possibly due to the drug Edwards and his colleagues (1956) mention 9 possible cases in 1 000 deaths associated with anaesthesia Ostlere reviewing the literature in 1953 commented the fairest decision seems to be that trichloroethylene can cause primary cardiac failure in the same way as chloroform but extremely rarely

Does this drug in fact carry an inherent danger? Be this as it may, trichloro ethylene deaths in the form of sudden cardiac arrest exemplify an important aspect of the anaesthetic death problem as a whole

When a drug is introduced into clinical practice undesirable side effects may be possible and eventually a death may occur This is reported, and the implica tions of the side effects fully discussed Now the circumstances which attend the occurrence of unexpected cardiac arrest are hardly ideal for the making of clear unhurried observations Further the difficulties of constructing a completely unbiased account of such an event are increased by the natural desire of the individual concerned to be able to state a cause for the fatality and maybe a cause independent of skill Hence there is a tendency not only to invoke any possibly relevant explanation already on record no matter how conjectural or hypothetical it may be but also perhaps unwittingly to suppress facts irrelevant to this particular explanation The difficulties of the situation resemble those so clearly described by Claude Bernard (1865) when commenting on the observer

indisputably demonstrated there is no reason why an occasional anaesthetic death should inevitably occur in no matter how large a series of administrations

Beecher and Todd (1954) give some figures for anaesthetic deaths associated with the use of thiopentone (all uses without curare) during the period 1948–52 There were 109 600 administrations in all with 72 deaths (1 1 522) The yearly figures are more instructive They show a death rate of 1 720 at the beginning of the period decreasing steadily to 1 3 400 at the end, a reduction by a factor of 4 7 It is difficult to believe that this improvement can represent anything other than increasing skill on the part of the administrators

Dundee (1956) made a list of the absolute and relative contra indications to the use of thiopentone A perusal of this prompts the observation that mistakes can arise through the misinterpretation of quantitative data relating to anaesthetic deaths which have been inadequately classified For example unless care is taken to prevent it general anaesthesia produced by any agent can be complicated by fatal respiratory obstruction No general anaesthetic drug is unique in this respect If anaesthetic mismanagement in this direction is common then the drug which is popular at the moment will be the one most commonly involved Unthoughtful interpretation of crude statistics in which such fatalities are included may give rise to an exaggerated view of the particular dangers of the drug concerned So much is obvious But the fallacy it represents can appear in more subtle forms

Macintosh (1949) pointed out that several agents in turn including the intravenous barbiturates have been described as being particularly deadly when given to patients already suffering from severe respiratory obstruction (the question was first raised *a propos* oedema of the glottis associated with inflammatory processes in the neck) He makes it clear that there is no need to invoke specificity Loss of consciousness from any cause means loss of the use of the accessory muscles of respiration In this lies the danger

THE NEED FOR FACTUAL DATA

Regurgitation or vomiting during anaesthesia has brought about many deaths This hazard in contrast to many of those already mentioned represents one which can be largely explained without invoking abstruse hypotheses Edwards and his colleagues (1956) give a classification of 110 fatal incidents They re-emphasize that this risk is particularly connected with acute abdominal conditions accident and obstetric cases Some comments on fatalities in the latter category will serve to illustrate what is perhaps the most important aspect of the whole problem

Parker (1956) recorded 3 048 forceps deliveries in domiciliary practice without a death due to vomiting During the same time there were 2 200 deliveries in one hospital in the same area with four deaths due to vomiting This significant difference ($p = 0\ 03$) demands explanation

It has been suggested that hospital cases always include a greater proportion of patients in poor general condition less likely to stand anoxic episodes *should* they occur it has however to be admitted that many healthy patients have succumbed to this complication Where vomiting is concerned *the lateral is safer* than the lithotomy position and the former is more commonly used in domiciliary midwifery practice The nitrous oxide–oxygen–ether sequence is customary in

It is certainly not the outcome of experiment. Fortunately it rarely causes serious harm.

It is also customary to give atropine to small, ill children in a dosage similar to, or only slightly less than, that used for fit adults. This is a departure from the accepted principle that dosage should bear some relationship to body weight and physical status. Maybe this exception is made because children tolerate atropine well. Data relating to convulsions during anaesthesia, and particularly from those cases in which temperature control was disregarded, throw doubt on the general validity of this axiom, and on the wisdom of following traditional practices of unproven value.

Another time honoured custom is to put unconscious patients in the lateral position only if they happen to be recovering from certain operations notably those on the nose, throat or mouth (Macintosh, 1949). If it were customary to put all patients recovering from general anaesthesia in this position (unless contra indicated) doubtless many deaths would be prevented. Deaths due to post operative respiratory obstruction have occurred through the unsatisfactory circumstances brought about in some hospitals by the shortage of trained nurses. These facts demand a reconsideration of the traditional view that the care of unconscious patients, in the immediate post operative period, comes reasonably within the province of a hospital's nursing staff.

QUANTITATIVE AND QUALITATIVE ASPECTS OF RISK

Dundee (1956) collected reports from various sources which showed that 67 deaths occurred in 192 281 administrations of thiopentone a mortality of 1 2,870. He pointed out that,

> it does not follow that one need encounter three to four inevitable deaths in each ten thousand administrations of the drug. No details of dosage rate of injection or of the pre operative condition of the patients are available for the fatal administrations but it is possible that many fatalities could have been prevented by the judicious use of the drug and a proper appreciation of its limitations.

If anaesthetic deaths have taken place in certain circumstances it is reasonable to say that those particular circumstances carried a risk. The word risk can be usefully used in such a context. But it appears to be not uncommon practice to attach to the word numerical values based on mortality, and then to use these numbers as though they were probabilities known *a priori*.

If a particular card is obtained as the result of making a single random draw from a mixture of twenty packs of playing cards it would be true comment to say that the probability of this event occurring was about 1 1,000. It would be equally true to say that this probability holds for similar procedures in the future. The risk of getting this card remains the same. When there is an anaesthetic death after thiopentone or, *mutatis mutandis* after any other drug it would not be true to say that the risk was 1 2 870. Comparable remarks are frequently reported as having been made in coroner's courts. Although this misuse of the language of numbers may be exemplary when offering condolences it cannot be construed as a justification for complacency. Unless inherent toxicity can be

generally used in these circumstances are concerned with conjectures and not with facts If facts were available and included information with respect to the status of the anaesthetist concerned they might show that the prevention of anaesthetic deaths is more an educational and administrative problem than a pharmacological one

ERROR AND RETICENCE

There has been repeated occasion to note that some anaesthetic deaths cannot be completely explained although there may be a more or less satisfactory hypothesis with regard to the manner in which death occurred, for example, as the result of reflex cardiac arrest We do not know, however, why such a complication should occur in one patient and not in some other apparently similar one exposed to seemingly similar circumstances Descriptions of fatalities of this kind and accounts of relevant research are not infrequent in the literature Fatalities where there has been lack of skill receive less publicity and manifestations of frank error are very rarely discussed except in such cases where there has been medico legal action In many surveys of anaesthetic deaths incidents of this kind are briefly dismissed under such nebulous headings as "gross errors of anaesthetic management Such vagueness or reticence is very understandable and may be desirable from some points of view and on some occasions but it is the negation of all progress towards the prevention of error

It has come to light that deaths have been caused by the injection of one of two drugs of widely dissimilar potency but with almost indistinguishable names Once it was established that such calamities occurred repeatedly the hazard was reduced by altering a name Deaths have occurred through the use of the wrong cylinder of gas A means has now been devised which if generally applied will make this hazard of historical interest only Deaths have occurred through the spraying of too much local analgesic solution into the air passages A new sprayer has been invented commendable on account of its efficiency even when used by the less thoughtful but safer in anyone s hands than the older appliances because it will not hold more than a safe quantity of solution

It is unbelievable that these, and a few similar examples represent the limit that can be reached by the application of ingenuity to the prevention of deaths due to error It would not be far wrong to suggest that the amount written about anaesthetic deaths is in direct proportion to the rarity of the form they take and the obscurity of the arguments needed to explain them Great progress might be made if it were generally recognized that the disclosure of error may be as helpful as the disclosure of ignorance The encouragement by the Association of Anaesthetists (1949) of the anonymous reporting of all types of fatalities has already produced promising results Liability to error is not a failing peculiar to anaesthetists and the prevention of fatalities due to mistakes might be achieved in ways other than through the sciences immediately basic to anaesthesia itself But ingenuity can never be applied to this problem unless the patterns of error are known

CONCLUSION

Some examples of death under anaesthesia have been considered but there are many other equally important ways in which this tragedy can occur These deaths

hospitals, open chloroform and ether are the rule in general practice Is it easier for the non expert to make a smoother induction with a chloroform–ether mixture, so that the number of patients at risk is less? Is it that anaesthetists of the younger *generation lack experience in making nitrous oxide–oxygen–ether inductions* a method which is seldom used nowadays except in obstetrical work? What pro portion of obstetrical anaesthesias are given by anaesthetists, what proportion by house surgeons house physicians or by junior members of the obstetric staff directed to undertake a procedure for which they have neither interest nor qualification? Even given the experience necessary to interpret them, it is unlikely that the signs of imminent vomiting during anaesthesia will always be noticed by someone whose interest is predominantly in the obstetric management of the patient

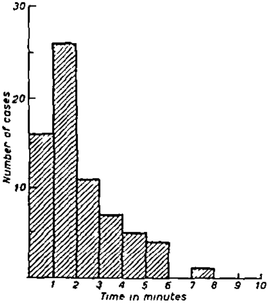

FIG 26—Onset of emergence vomiting after obstetrical anaesthesia

Emergence vomiting occurred in 70 of 100 consecutive patients lightly anaes thetized with nitrous oxide–oxygen–ether for episiotomy and forceps delivery The time interval between the removal of the facepiece and the onset of vomiting was noted and is recorded above The average duration of anaesthesia was 32 minutes With deeper and longer anaes thesias the interval before emergence vomiting is likely to be longer

How often does emergence vomiting bring about this type of fatality? The time of occurrence of this phenomenon can be noted (Fig 26) It could be inferred from such data if they are representative of the general situation that potentially dangerous emergence vomiting takes place very soon indeed after the mask is removed Hence what experience and what degree of competence has been attained by an individual who when giving an account of a fatality from this cause uses such words as after a few minutes I was called back and found ? What proportion of the anaesthesias in hospitals has to be given by inexperienced doctors and how much instruction in practical anaesthesia did these doctors receive in their undergraduate days?

We can take it as axiomatic that skill is the greatest single factor in the prevention of anaesthetic deaths Can it be that the elementary mistake is still being made of laying undue emphasis for misfortune on drugs and mere mechanical appliances to the virtual exclusion of the prime importance of the human factor in these matters?

Practically all the foregoing remarks which may be taken as typical of those

CHAPTER 16

HYPNOSIS

A A MASON

TODAY a vast amount of literature is emerging both in England and the United States of America on the uses of hypnosis in medicine psychiatry and anaesthesia In this short chapter the application in anaesthesia is summarized, together with some of the dangers associated with its use, it must be emphasized however that a chapter like this merely serves as a superficial introduction to a vast subject Students wishing to practise hypnosis would be well advised to read the books written by Wolberg (1948) Brenman and Gill (1947), le Cron and Bordeaux (1949)

SUSCEPTIBILITY TO HYPNOTISM

Susceptibility to hypnosis bears no relationship to the sex race, profession or intelligence of the subject Broadly speaking if the patient is accessible he can be hypnotized, and it has nothing to do with will power or 'weak mindedness Some of the best subjects are often highly intelligent and very self willed but they must be persuaded to co operate in the induction The patient whose fear or aggression makes him uncooperative cannot be hypnotized From the time they are first able to understand language and simple instructions the very young are excellent subjects, as are those in their teens Elderly patients are more difficult to hypnotize if they are deaf for the method of induction is so frequently vocal

With an adequate technique, there is success in approximately 90 per cent of cases The 10 per cent of failures may be hypnotized by another hypnotist and are probably due to some incompatibility between patient and hypnotist Therefore nearly 100 per cent of people are hypnotizable by someone or another This seems to imply that hypnosis is a normal perhaps physiological state which we can all experience from time to time This will seem less strange if it is appreciated that most people have probably experienced hypnotic states without realizing their nature for example when lulled to sleep by the rocking of a train ship or hammock or by the monotonous stimulation of a lecturer, or a masseur

The production of hypnosis may be summed up as follows It is a trance like state produced by repeated rhythmical monotonous sensory stimulation The stimulation may be auditory voice music or any monotonous sound visual a flickering pattern swinging pendulum or light, or tactile stroking of limbs face or head

can be classified by diverse methods, but there is one way which is both simple and relevant to this final approach This is merely a division of fatal cases into two types those for which a reasonably satisfactory explanation can be provided, and for which effective counter measures are practicable, and those which cannot at present be fully explained, and for which counter measures are either lacking or largely empirical

It follows that there are a number of essential requirements for the prevention of such deaths as for example (1) the encouragement, by some means or other of the direct or indirect reporting of detailed accounts of fatalities, (2) the widest dissemination of such useful information as can be derived from these accounts, and its inclusion in a prominent position in teaching programmes, (3) a restriction of the practice of unsupervised administration of anaesthesia by newly qualified doctors and (4) the application of research not only to the elucidation of the more obscure aspects of the problem but to the prevention of fatalities of the types that are already understood

The modern trend is towards the recognition that the prime prerequisite is the collection of factual data Only a fool learns by his own experience No saying could be more apt to the present context

REFERENCES

Association of Anaesthetists (1949) *Anaesthesia* 4 203
Beecher H K (1954) *Lancet* 2 922
— and Todd D P (1954) *Ann Surg* 140 2
Bernard C (1865) *Introduction to Experimental Medicine* Transl by H C Greene (1927) New York Macmillan
Brown G (1950) *Royal Adelaide Hosp Rep* 30 27
Dawkins C J M (1956) *Brit med J* 2 995
Dundee J W (1956) *Thiopentone and other Thiobarbiturates* Edinburgh and London Livingstone
Edwards G Morton H J V Pask E A and Wylie W D (1956) *Anaesthesia* 11 194
Hewer C L (1956) Personal communication
Hewitt F W (1912) *Anaesthetics and their Administration* London Macmillan
Hunter A R (1956) *Brit med J* 2 919
Macintosh R R (1949) *Brit J Anaesth* 21 107
Ministry of Health (1954) *Report* Part Two London H M Stationery Office
Ostlere G (1953) *Trichloroethylene Anaesthesia* Edinburgh and London Livingstone
Parker R B (1956) *Brit med J* 2 16
Registrar General s Review (1953) *Statistical Review of England and Wales Text Medical* London H M Stationery Office
Report (1956) *Working Party on Anaesthetic Explosions* London H M Stationery Office
Stephenson H E Reid L C and Hinton J W (1953) *Ann Surg* 137 731

The direct eye gaze method

In this method the hypnotist gazes directly into the patient's eyes making all the while suggestions of heaviness drowsiness sleep and so on It does not appear to be a very successful method for English people, probably because of an immediate resistance in the race to being told authoritatively what to do This kind of authoritative method is excellent for children who become restless and impatient with the slower forms of induction

Other methods

Other methods of trance induction employ the use of mechanical devices such as rotating discs and metronome like appliances There is however no substitute for the human voice which can be varied to suit each patient Above all the student should eschew any form of mumbo jumbo darkened rooms mysterious passes and all the tricks of the stage hypnotist These are undignified and unnecessary and cause only ridicule and disrepute

It is possible to use drugs to aid the induction of hypnosis Sodium amylobarbitone has been used both orally 1–3 grains, and intravenously, 250–500 milligrams Scopolamine $\frac{1}{150}$ grain is one of the most effective drugs and makes the induction of hypnosis very easy Induction of hypnosis in a new patient takes approximately 10 minutes and if there is failure to induce hypnosis after the second attempt, then it is probably wiser to abandon the attempt The failure is due to unconscious resistances in the patient which are difficult to defeat and outside the realm of anaesthesia

TRANCE DEPTHS

Just as there are varying depths of anaesthesia, so are there varying depths of the hypnotic state The depth of the anaesthetic state depends on the quantity of various chemicals in the body The depth of hypnosis, on the other hand is related to the personality of the person being hypnotized and to the skill and technique of the hypnotist It may even vary in the same patient on different occasions dependent to some extent on mood The depth achieved on the first induction is less than that on subsequent inductions and the final depth possible is usually not achieved until several inductions have been performed The trance state has three divisions light medium and deep hypnosis Of patients 35 per cent will go into a light trance 35 per cent into a medium trance and 20 per cent into a deep trance It is important for the anaesthetist to distinguish between these levels of hypnosis When the patient's eyes close involuntarily and in response to suggestion then it can be assumed that the patient is at least in a light trance The eyelids close in the manner typical of the cataleptic eyelids Simple suggestions are then made to the patient for example your right hand will get lighter and float up into the air If the patient responds to these suggestions he is probably in a medium trance state If he fails to respond he has not progressed beyond the light trance state The best method of determining the depth is by testing with pin prick Suggestions of analgesia are made such as Your right arm is becoming cold and numb and you will feel no pain The patient is then tested gently with a needle If he reacts immediately he is in a light trance If he allows some penetration but winces or moves when a more painful stimulus is applied then a medium trance has been

METHODS OF TRANCE INDUCTION

The hand levitation method

In the hand levitation method, the patient sits in a comfortable chair or lies down, he is then told to concentrate all his attention on one hand. Suggestions are then made that the fingers will move and after that the hand will get light and float into the air. These suggestions are repeated over and over until normal movements occur in the patient's fingers, and these normal movements are incorporated within the hypnotist's suggestions as though he had suggested them. The patient then feels that the movements have occurred because of the suggestion that they would occur. It is then suggested that the hand is getting lighter and will float up and reach the patient's face and when it does so the patient will go into a deep sleep. The whole procedure generally takes 10–15 minutes. It has the advantage of proceeding at the rate that the patient himself determines by his hand raising. The induction may be lengthy and cannot be forced along by being more directive, which makes the method of little use in anaesthesia where time is limited. A more detailed account of this excellent method is given by Wolberg (1948).

Hypnosis by eye fixation

The patient is seated in a comfortable chair or lies on a couch. His eyes are fixed on a spot slightly behind and above the hypnotist's head. This can be a light or a spot on the ceiling. As the patient gazes at this fixedly generalized suggestions of tiredness, heaviness and drowsiness are made, and more specific suggestions are made such as that the eyelids are getting heavier and tired (which of course they will do physiologically), and the hypnotist continues with rhythmical repetitive suggestions until the patient goes into a hypnotic trance. Here is part of a verbatim report of such an induction:

> You are getting drowsy and heavy, your eyes are tiring and watering, you are blinking more and more. Your lids are getting so heavy that they want to close. Relax and think about sleep. Your eyes are watering, your lids get heavier and heavier. Your eyes are tired and presently they will close. Keep thinking about sleep, how nice it would be to sleep. You notice you are getting sleepier and sleepier. Keep looking at the spot. You are feeling your eyelids getting heavier and heavier—more and more tired. Now they are closing and now your arms and legs are heavy as lead and a drowsy feeling spreads over you. You are relaxing and going to sleep. Relaxing and going to sleep. Breathe deeply and slowly, with each breath you sink nearer and nearer to sleep. Your eyes are heavy and sleepy, they are closing up, closing up, closing up.

Repetitive suggestions for several minutes usually result in a closure of the patient's eyes involuntarily. If the patient's eyes do not close, very often a firm command to close them will produce the desired result. When the eyes close involuntarily and in a progressively rapid blinking fashion, the hypnotic state is reached. This phenomenon, the eye blinking more and more rapidly and then closing in a flutter, is known as the cataleptic eyelid. It is quite distinct from voluntary closure of the eyes and is a reliable sign that the hypnotic state has been achieved.

cystoscopy and a host of manipulations with surgical instruments can cause anxiety and distress in many patients and can be comfortably performed in the hypnotic state Hypnosis for cardiac catheterization can be very useful It does not embarrass the inefficient heart and permits use of chemical anaesthesia only for the major surgical procedures thus enabling the cardiac patient to husband his slim resources for such times Goldie (1956) showed how this depth of hypnosis can be utilized in the casualty department, particularly for the emergency with the full stomach

Deep trance hypnosis

In deep trance hypnosis analgesia is considerable and extensive surgery can be performed Mason (1955) reported a second stage mammaplasty, and in 1957 an abdominal scar herniorrhaphy under hypnosis Amputations of limbs can be performed, impacted wisdom teeth have been removed in Great Britain many times and reports from the United States of America of caesarean section, appendicectomy and thyroidectomy have appeared in the last few years (Kroger and DeLee, 1957) The advantages of surgical procedures without any anaesthetic being given are obvious The toxic effects of anaesthetic drugs are absent, and hypnosis can be used in severely ill patients in whom chemical anaesthesia is contra indicated Shock is minimized, and protective reflexes, apart from those which have been specifically removed, are present Accidents are therefore less likely to occur, and ulnar nerve pressure, brachial root traction, and burning with hot fluids would be felt by the patient and brought to the notice of the surgeon The cough reflex is present therefore blood and vomit cannot be inhaled, and oral procedures are facilitated and rendered free from anxiety The patient can drink fluids during the operation and post operative pain or discomfort can be prevented by suitable suggestion The patient can be made immediately ambulatory if desired and chest complications therefore minimized Post operative nausea and vomiting can also be eliminated

This would be an ideal form of analgesia were it not for the fact that not more than 15–20 per cent of cases can be anaesthetized in this way for major surgical procedures, and the impossibility of forecasting good hypnotic subjects beforehand Emergency procedures are almost completely ruled out The certainty and safety of chemical anaesthesia today has relegated the use of hypnosis for major surgical procedures to a very minor place

HYPNOSIS AND BURNS

Crasilneck and his colleagues (1955) have treated severely burned patients with the aid of hypnosis It is used as a method of anaesthesia for debridement dressing changes and skin grafting and the obviation of repeated chemical anaesthesia is of great value in these very toxic patients Post hypnotic suggestion can be utilized to allay post operative pain This enables early ambulation decreases chest compli cations and minimizes contracture formation Food intake is another problem in the severely burned case because of pain depression toxaemia and nausea The use of hypnotic suggestion directly and post hypnotically has been used to elevate the calorie intake from 1 000 to 8,000 calories daily

achieved If the skin can be penetrated completely with no reaction from the patient, a deep trance has been achieved

These tests are rough guides to depth, and as in chemical anaesthesia, experience is the only sure guide It is infrequently realized that analgesia is not an automatic concomitant of hypnosis, and even though the patient is in a deep trance there is no analgesia unless it is suggested directly Words such as numb and frozen are apt to be ambiguous and the phrase "you will feel no pain ' should always be inserted to make sure It must also be emphasized that the anaesthesia produced does not follow the lines of neurological distribution It occurs specifically in areas which are suggested, and these areas must be clearly outlined, for example the suggestion your jaw will become anaesthetic is valueless because the patient will not know whether the upper or lower jaw is meant and the lay concept of jaw differs vastly from the anatomical concept However if it is suggested that your hand below the wrist both back and front will become insensitive to pain , then it is clear to the patient which area he is expected to anaesthetize and he will do so accurately Again, areas such as the back or the stomach are impossible to delineate in a patient s mind The area might be swabbed with spirit or water so that the patient feels, and in consequence knows exactly the area to be anaesthetized

Light trance hypnosis

Although analgesia does not exist in the light trance state, this depth of hypnosis *can find considerable use in the practice of anaesthesia It is particularly* useful in the removal of the psychological overlay of pain, as for instance in the patient who does not go to the dentist because of fear rather than any anticipation of pain the patient who is terrified of a local or general anaesthetic or in particular the patient who still complains of pain despite an adequate local or regional block These patients are filled with fears and anxiety, and their minds translate touch or any physical sensation into pain because of the overlying fear If they are put into a light trance state and then local or general anaesthesia is induced an excellent result ensues Light trance hypnosis is an excellent premedication for general anaesthesia It ensures freedom from anxiety and a smooth induction phase and is particularly useful for dental anaesthetics It is also an effective adjuvant in the case of the patient who must undergo extensive surgical procedures under local or spinal analgesia

Medium trance hypnosis

Here varying degrees of analgesia are present and tests should be performed to find out the extent and depth Procedures should never be attempted which require a greater depth than that which exists This destroys the patient s confidence and prevents the utilization of even the limited benefit present Medium trance is a useful depth for repeated procedures which do not warrant general anaesthesia Examples of these are repeated manipulations, orthopaedic and physiotherapeutic urethral instrumentation thoracic and abdominal exploration and lumbar puncture Ward procedures like mastoid antral and burn dressings can be done with very little pain and discomfort in the medium trance state Multiple dental fillings are eminently suitable to be carried out under this depth of hypnosis since they require repeated local blocks which may be more painful than the fillings themselves Procedures like sigmoidoscopy, gastric lavage and aspiration antral puncture

CHAPTER 17

ANAESTHESIA AND DISEASE

O P DINNICK

OPERATIONS are performed today which twenty years ago would have been considered unjustified owing to the diseased condition of the patient Improved anaesthesia blood transfusion chemotherapy and particularly the regulation of fluid and electrolyte balance have all contributed to this improved situation No longer are patients subjected to long periods of bed rest before operation and early post operative ambulation is encouraged This not only tends to prevent circulatory stagnation and thus diminish the likelihood of pulmonary embolism and atelectasis but also benefits the morale of both patients and ward staff alike

INFECTIONS

Bronchitis and the common cold

The common cold may well be a precursor of pneumonia and is a condition which undoubtedly predisposes to post operative pulmonary complications (Harris 1951) Harris also again drew attention to the important point that such complications were frequent after operations which predisposed to post operative atelectasis such as abdominal or other procedures which interfered with breathing and coughing Palmer and Sellick (1953) further emphasized the connexion between upper respiratory tract infections bronchitis and post operative chest complications Besides stressing these relationships they clearly showed the importance of reducing the patient s sputum production to a minimum before operation Post operative breathing exercises alone were insufficient an energetic regime of postural drainage and active coughing combined with the use of bronchodilator drugs is essential for a few days before and immediately after surgery

It is sometimes argued that post operative pulmonary complications may be controlled by modern antibiotics but Palmer and Sellick (1952) had previously shown that routine penicillin cover without active steps being taken to assist the elimination of sputum did not reduce the incidence of atelectasis, even though the secondary infection was controlled A sanguine attitude to the powers of antibiotics and the development of drug resistance in bacteria is obviously justified in all emergency surgery but it should not be allowed to cloud the clinical assessment and appropriate preparation of patients for elective operations

For assessment there are three broad groups of patients but every case must be considered on its merits First there is an obvious group in which a cold is a clear contra indication to operation either because of the site of the operation

HYPNOSIS AND OBSTETRICS

Good obstetric analgesia has many requirements to fulfil It may have to be prolonged for hours or days and so must be of low toxicity It also needs to be powerful enough to give relief from the severe pain of the second stage without depressing either uterine contractions or the infant s respiration Hypnosis fulfils both these requirements excellently Potent local or general anaesthesia needs expert administration and this is not available for most deliveries, but hypnotic analgesia is eminently safe and frequently more effective than nitrous oxide and air, trichloroethylene or pethidine Many of the complications of labour are due to delay in one of its stages The delay itself is frequently secondary to anxiety, fear and pain which can all be lessened by the use of hypnosis thus reducing its incidence and sequelae Hypnosis is especially valuable in cases of toxaemia of pregnancy or cardiac failure

The fact that the mother is conscious at the time of her delivery is thought to have great psychological importance for the future mother–child relationship

PHYSIOLOGICAL ASPECT

The physiological mechanism which is responsible for the production of analgesia in hypnosis is not clear Some research workers believe it to be allied to distraction anaesthesia and some believe that there is a blockage of pain impulses at the synaptic junctions Some patients being operated on under hypnosis show no elevation of pulse and respiration or fall in blood pressure suggesting that the pain is not being appreciated centrally Other patients exhibit pulse, respiratory and blood pressure changes, but say afterwards that they experienced no painful or unpleasant sensations In these cases there has undoubtedly been central appreciation of pain but the amnesia produced by the hypnotic state removes this from consciousness It is as yet undecided whether there can be pain in the organic or surgical sense if there is no consciousness of it Research being carried out at the present moment will, it is hoped, clarify this point However, electroencephalogram recordings of patients being subjected to painful stimuli in the hypnotic state resemble closely recordings of patients subjected to painful stimuli under general anaesthesia This, of course, supports the contention that the anaesthesia is real and not simulated or hysterical

BIBLIOGRAPHY AND REFERENCES

Brenman M and Gill M M (1947) *Hypnotherapy* London Pushkin Press

Crasilneck H B Sturman J A Wilson B J McCranie E J and Fogelman M J (1955) *J Amer med Ass* 158 103

Le Cron L M and Bordeaux J (1947) *Hypnotism Today* New York Grune and Stratton

DeLee J B and Greenhill J P (1939) *Yearb Obstet* p 164

Goldie L (1956) *Brit med J* 2 1340

Kroger W S and DeLee S T (1943) *Amer J Obstet Gynec* 46 655

— — (1957) *J Amer med Ass* 163 6

Mason A A (1955) *Anaesthesia* 10 295

— (1956) *Proc R Soc Med* 49 481

— (1957) *Abdominal Hermorrhaphy under Hypnosis* (In Press)

Michael A M (1952) *Brit med J* 1 734

Sampion R L H and Woodruff M F A (1946) *Med J Aust* 1 393

Wolberg L R (1948) *Medical Hypnosis* Vols 1 and 2 New York Grune and Stratton

condition requiring surgery, and by the accompanying operation The chances of this occurrence are more difficult to assess, but chemotherapy has reduced them to reasonable proportions moreover, the surgical condition frequently compels acceptance of the risk

Patients with sputum must be treated with postural drainage as previously described and chemotherapy commenced In favourable cases the sputum will become negative for acid fast bacilli, and the disease arrested sufficiently in a few weeks to permit operation Patients with healing foci or early cases with no sputum or with sputum free from tubercle bacilli may safely be given a general anaesthetic In these cases it is important to avoid violent respiratory movements which may break down walled off areas of partly healed disease If chemotherapy cover is given to these less severe cases it must be continued for several months Finally, the risk of infecting hospital staff and apparatus must not be overlooked and full nursing precautions must be taken until the sputum can be shown to be free from tubercle bacilli

Sterilization of Equipment

The sterilization of anaesthetic equipment or even the effective cleaning of such items as corrugated tubing and one way valves sets a problem to which no satisfactory solution has yet been found Sterilization by heat is accepted as being the method of choice whenever possible, but its application to anaesthetic apparatus and equipment is either impracticable or else shortens the life of rubber equipment to a degree that makes its routine employment economically unacceptable

The practical difficulties of solving this problem and the apparent absence of serious sequelae when absolutely sterile equipment is not used, have perhaps engendered a casual attitude to the subject Ziegler and Jacoby (1956) found that anaesthetic machines in daily use were heavily contaminated with organisms—especially round the facepiece connexions—but failed to demonstrate their transmission from an anaesthetic machine bag to an experimental rubber lung

Smith (1957) reported that slices of rubber from an endotracheal tube could inhibit the growth of staphylococci under certain *in vitro* conditions the importance of this observation lies not so much in that it may perhaps partly account for the absence of cross infection in the past, as in that the newer synthetic plastic materials may not possess this bacteriostatic property Nevertheless there seems little doubt that cross infection by contaminated anaesthetic apparatus can occur, though judging by the scarcity of reported incidents it is uncommon presumably because patients with a virulent respiratory infection seldom come to surgery It has been suggested that influenza might have been transmitted in this fashion (*J Amer med Ass* 1937) and Livingstone and his colleagues (1941) reported the spread of tuberculous infection by contaminated face masks More recently Joseph (1952) described an epidemic of tonsillitis in which the anaesthetic machine was suspected as the infecting agent and this report cast doubt on the previously held belief (Waters 1931) that soda lime was an effective bacterial trap

Although Magath (1938) devised a water bacterial trap for closed circuit machines any effective filter must inevitably be bulky and materially increase the resistance to respiration moreover no matter how efficiently it may absorb bacteria it is not possible to protect against a virus infection by this method

as for example the nose or eye, or because it is a purely cosmetic operation in which clearly no risk is justifiable

A second group of cases comprises those in which the likelihood of post operative chest complications is remote, such as operations on the arms Here undoubtedly, the risk of operating in the presence of a cold is slight (Ellis, 1955) but there are nevertheless, reasons for counselling caution One is the unpredictability of the disease, and the likelihood that any subsequent pneumonia would be blamed, perhaps rightly, on the anaesthesia secondly, that the cause of any post operative pyrexia is made more difficult to diagnose, and thirdly, that a patient may not tolerate well the added discomfort of even a minor operation while suffering the misery of a severe cold

The third group consists of patients who, because of the site of the operation the presence of bronchitis or other pulmonary disease or of a history of previous post operative chest complications demand most careful consideration Here the *operation may justifiably be postponed because of a cold, which will almost* invariably exacerbate a pre existing bronchitis It is difficult to predict the course of any cold in an individual but some guide may be obtained by knowledge of a particular epidemic, either in the hospital or in the patient s home or place of work A two day sniffle ' may be ignored but other strains of virus produce more serious upsets If a patient states, as is not infrequent, that a cold always goes to his chest, and if a further questioning elicits that this is always accompanied by increased sputum for three weeks or so then an operation such as gastrectomy should clearly be delayed, and the best course may be to discharge him from hospital for that period On the other hand if no such history is obtained two or three days postponement may be sufficient The common cold is a serious condition in a bronchitic patient and delayed resolution and bronchiectasis may follow pneumonia It is wise to be cautious

Pulmonary tuberculosis

The successful operative treatment of pulmonary tuberculosis in many clinics under a variety of general and local anaesthetic techniques, and the effectiveness of chemotherapy, have together revolutionized the approach to this disease Many patients are now confidently accepted for surgery both of the lung and for inter current conditions who in the past would have been denied active therapy and doomed to long months of expectant treatment

Outside the thoracic surgical centre frequently a routine pre operative radio graphic examination of the chest reveals a suspicious tuberculous infiltration Unfortunately activity cannot always be diagnosed with certainty from one film, or in one clinical examination Cases for elective operation must of course be postponed for investigation but in many there is a fair degree of surgical urgency, and the risks of operation must be briefly considered The immediate and most serious risk is that of an inhalational tuberculous bronchopneumonia or of secondary infection in a post operative atelectasis Such direct spread of the disease should largely be avoidable by careful anaesthetic management and pre operative reduction in the amount of sputum but if this be not possible and the surgical condition demands immediate operation regional analgesia is strongly indicated, so that an active protective cough reflex may be preserved

The later risk is of exacerbation of the disease by the metabolic stress of the

this reason are widely recommended and used for diabetic patients Too much stress however, can be laid on the hyperglycaemic effect of the drugs used in anaesthesia

Prolonged pre operative starvation has been abolished, emotional stress reduced by premedication, and the excitement stage circumvented by thiopentone Hypoxia is never tolerated under modern conditions and carbon dioxide elimination is ensured by controlled ventilation and fluid balance is maintained and post-operative vomiting greatly reduced These many factors combine to make a modern anaesthetic even one in which a little ether is used relatively little disturbing to carbohydrate metabolism when compared with that of twenty years ago and it would seem reasonable to view with caution any recommendations based on observations made at that time Clinical experience supports this view, and the author has not seen any case complicated by hyperglycaemic coma but, on the contrary hypoglycaemia has been a greater worry, especially when glucose has been given by mouth and presumably not been absorbed

Although the blood sugar level is not seriously disturbed by a well given anaesthetic in a fit patient (Griffiths 1953), the diabetes may be made worse by other factors such as dehydration infection persistent vomiting and the metabolic response to trauma In most cases the total effect of the illness and operation is exacerbation of the disease Some patients become resistant to insulin and in all insulin requirements are increased This requirement may vary very greatly in the immediate post operative period and after a major operation the patient may not become stabilized until as late as the fourteenth day Because of this rapid and in some cases extreme fluctuation of insulin requirements a quick recovery from the anaesthetic is very desirable so that one of the possible causes of post operative coma may confidently be excluded

Stabilization

Facilities for accurate blood sugar estimations in a laboratory should always be provided when operation is contemplated on a severe diabetic but when such a service is not readily available use may be made of a simple bedside method of estimating blood sugar which has proved to be of great value in the treatment of emergency cases (Davies and Paley 1957 Osborn 1957) However as explained below in most cases the insulin dosage may be adjusted according to the urine sugar levels

Before operation the longer acting insulin should be stopped and the patient stabilized on soluble insulin whenever possible This may take 48–72 hours and this time should always be made available for severe diabetics who are to undergo major surgical procedures The oral insulin substitutes of the sulphonamide group should never be used at such a time The time taken for absorption of orally administered drugs is always uncertain and may be considerably delayed by apprehension and narcotics such as morphine or pethidine (La Salvia and Steffan 1950) and this uncertain absorption applies equally to food and hyper tonic glucose solutions This knowledge has been emphasized by the recent report of the Association of Anaesthetists Committee on Anaesthetic Deaths (Edwards and his colleagues 1956) which showed that the inhalation of vomit was one of the most important causes of death associated with anaesthesia Moreover it was made clear that the proportion of diabetics dying from this cause was considerably

The lack of information on the vulnerability or otherwise of viruses must not be forgotten when considering chemical methods of sterilization. Many compounds have been employed for this purpose, only a few of which are effective in a reasonably short time, but the risk of irritation and contact burns from chemicals remaining in the rubber in spite of repeated washings, has resulted in most of them being abandoned for use with anaesthetic equipment. The common practice is to rely on washing and, where possible, scrubbing with soap and water.

This simple measure is, in any case, an essential preliminary to any further chemical sterilization and has been shown (Joseph, 1952) to produce a hundred fold reduction in the bacterial count in anaesthetic equipment. This author reported a further ten fold reduction in the bacterial count when hexachlorophene and a detergent were used instead of soap and he advised the employment of such a substance for the routine cleaning of anaesthetic rubber equipment, a recommendation which has been endorsed by McDonald Welch and Keet (1955) but as Ziegler and Jacoby (1956) stress, to be effective such treatment must be carried out immediately after the equipment has been used and before any secretions have time to dry.

A product readily available in Great Britain which would appear to be very suitable for this purpose is a mixture of 0·5 per cent cetrimide and 1:2,000 chlorhexidine (Hibitane) which is detergent nonirritant and effective against a wide range of bacteria. Though this solution will inhibit the growth of *Mycobacterium tuberculosis* a 0·5 per cent alcoholic preparation of chlorhexidine is required to kill this organism. Nevertheless until this promising drug has been proved effective on anaesthetic equipment in routine use it would be wise to rely on sterilization by heat so far as possible particularly after such equipment has been used on patients with open tuberculosis or other acute infective diseases.

The introduction of equipment and apparatus that can be easily cleaned and repeatedly sterilized by heat is a challenge to our designers and manufacturers which should not be overlooked.

DIABETES MELLITUS

This common disease with an estimated incidence of 6 per 1,000 in Great Britain (*Lancet* 1953) has in the past given rise to much confusion of thought and unnecessary concern in relation to anaesthesia. Much of this has arisen because of attempts to lay down detailed schemes of treatment where the insulin dosage was adjusted according to anaesthetic agents or the nature of the operation and also because of a failure to stress the wide variations in the type and severity of the disease itself.

Carbohydrate metabolism

The approach to the subject has not unnaturally been affected by the rise in blood sugar which has frequently been observed both in animals and in man after the administration of narcotics (Harris 1951). Moreover, in the past ketosis was also not infrequently an additional sequel to ether and chloroform anaesthesia (Minnitt 1933). Thiopentone cyclopropane and nitrous oxide are drugs which produce much less disturbance of carbohydrate metabolism, and for

of unconsciousness is only a few minutes, it is necessary only to omit the insulin for the one missed meal, for the equivalent glucose may be left out without grave risk. It is however preferable even in the diet only group to give some insulin, say 10 units and 25 grammes of glucose intravenously, if the operation is of any magnitude. This may be repeated in the post operative period for as long as necessary checking the insulin dosage from the urine tests.

It is customary to arrange that where possible the diabetic patient is placed first on the list and it is obviously desirable that major procedures on severe diabetics who are going to need close and skilled post operative supervision should not be performed too late in the day. However, as most of the less severe diabetics are usually stabilized with a morning and evening dose of soluble insulin it is often simplest to arrange a minor operation for these cases at about midday. They may then have a normal or light breakfast with insulin dosage adequate to cover this (that is less than the usual morning dose) and they should have recovered sufficiently to take their usual evening meal. Operating schedules are, however frequently disturbed but this need cause no alarm provided no injection of insulin is given in the ward with the ordinary premedication and the obsolete practice of relying on glucose by mouth is abandoned. This dose of insulin should be postponed until the patient is anaesthetized with an intravenous glucose drip running satisfactorily. Any inadvertent hypoglycaemia is thus avoided should the operation be unexpectedly delayed. A short period of hyperglycaemia is harmless in the absence of ketosis.

Hypothermia and hypotension

Two anaesthetic techniques demand special consideration. In hypothermia the metabolism of glucose is apparently inhibited below 31° C, and therefore glucose must be administered intravenously with caution. Blood sugar levels as high as 1,000 milligrams per cent have thus inadvertently been reached in non-diabetic patients (Wynn 1954). Griffiths (1953) on the other hand has shown that hexamethonium, when used to induce hypotension during anaesthesia, will lower the blood sugar in both normal and diabetic patients. Moreover, the action of insulin is greatly potentiated under these circumstances and a profound hypoglycaemia is easily produced. This is the more serious because the classical signs of this condition, pallor, sweating tachycardia, dilated pupil and twitching may be masked by the anaesthesia and sympathetic block. If, as Griffiths suggested this insulin sensitivity is a direct result of the sympathetic block inhibiting the release of adrenal medullary hormone in response to nervous stimulation, it can be expected to occur with some other drugs and methods of induced hypotension.

Conclusions

In conclusion the principles of management may be repeated, *the aim being to* disturb the patient s metabolism and dietetic habits as little as possible.

(1) Pre-operative stabilization on soluble insulin.
(2) Pre operative glucose never to be given by mouth.
(3) Administration of intravenous glucose in place of missed meals with appropriate insulin during and after all but the most minor procedures in mild cases.
(4) Avoidance of dehydration and salt depletion.
(5) Close post-operative supervision with 4 hourly to 6-hourly control of insulin

higher than the proportion of diabetics at risk There is no doubt that this resulted largely from the custom of giving pre operative glucose by mouth Personal experience of several similar cases, fortunately without a fatal outcome, and the knowledge of two unpublished deaths, reinforces the conclusion that oral hyper tonic glucose solutions should never be prescribed before operation It is said that isotonic glucose is of less risk, and this may be so in patients of a phlegmatic temperament, but the amount of glucose that can be administered in this way is limited and it is better given intravenously

King (1957) has dealt at length with this problem, and corroborates the con clusion that pre operative oral glucose is unnecessary and dangerous

Regime

No detailed regime can be laid down for all situations and each case will be an individual clinical problem, but the question of who is to be in charge of the diabetic management of the patient must be clearly defined In practice most patients will be found to fall into one of the following groups, (1) severe diabetics, usually young, who should be admitted to hospital for close supervision, irrespective of the nature or severity of the operation, (2) mild diabetics that is, those well stabilized on less than 40 units of insulin a day, who will usually need similar treatment if a major procedure is contemplated (3) mild diabetics (as above) for very minor operations, (4) diabetics controlled by diet alone, and (5) diabetics *of the first three groups for emergency operations*

When stabilization on soluble insulin has been effected pre operatively it is relatively simple to estimate the glucose and insulin requirements over the period when the patient is unable to feed himself A satisfactory ratio is to give 1 unit of insulin for every 2 5 grammes of glucose administered intravenously In most cases, the calorie intake will be limited by the amount of isotonic glucose required to maintain an adequate fluid balance, and the insulin dosage must be adjusted accordingly Only in exceptionally severe cases where there is already ketosis will it be necessary to give extra glucose in hypertonic solutions This should be avoided if possible as these strong solutions tend to cause venous thrombosis

In the absence of dehydration and salt depletion both of which should be assiduously avoided it must be remembered that dangerous hypoglycaemia may be produced more rapidly than extreme hyperglycaemia It is therefore wiser to err on the side of the latter during the immediate post operative period, when the patient s level of consciousness is likely to be impaired by powerful analgesic and narcotic drugs This is particularly important in emergency surgery where it is not uncommon to find that the patient has been given his insulin but has either not had the equivalent meal or has vomited it This information should always be sought when taking the history It may often not be possible to elicit accurate details of this kind and it is then that a blood sugar estimation may be of great value

In the immediate post operative period if adequate fluid has been given it should not be difficult to obtain enough urine from the sugar content of which the next dose of insulin is calculated but exceptionally a blood sample may be required The effect of this dose may be assessed after 4-6 hours by a further urine test and the amounts of subsequent injections adjusted accordingly

In the milder cases or even in some of the more severe ones where the period

the basic principle is to provide extra corticosteroid usually cortisone to cover the stress of the operation and more particularly the post operative period This must be given by injection immediately before operation and continued until absorption can again be guaranteed by mouth After a few days, the extra cortisone may be gradually reduced until a suitable maintenance dose is attained or resumed Patients on these high doses of cortisone have greatly reduced powers of resistance to infection and prophylactic chemotherapy is usually indicated but the greater risk is of a hypotensive crisis and strict attention must be paid to the details of fluid and electrolyte balance which is very unstable in these cases Nevertheless the blood pressure may fall to dangerously low levels in spite of apparently adequate supportive treatment It may be that the cortisone is not adequately absorbed or properly utilized and in these circumstances intravenous hydrocortisone has been found of great value This drug being in alcoholic solution must be considerably diluted before being injected but this may be obviated by the use of a recently developed water soluble derivative hydrocortisone hemisuccinate Now that the value of hydrocortisone has become appreciated noradrenaline is less often required to control these hypotensive crises

A full review of the problems of anaesthesia in adrenocortical insufficiency has been published by Dundee (1957) An increasing number of patients now being presented for surgery have been treated with corticotrophin or the steroid hormones for various conditions and it is important that this possibility be always borne in mind As de Mowbray (1957) has pointed out in a comprehensive review, the risk of post operative adrenal failure is still present for as long as 2 years after steroid therapy has been withdrawn

THYROID DISEASE

Thyroid disease has ceased to be a major anaesthetic problem, though each case needs careful assessment and management Adequate preparation with iodine and sedatives generous premedication non toxic anaesthesia and the application of the principles of fluid balance and temperature control have removed the aura of mystery and most of the dangers of the thyroid crisis while the relaxants enable intubation to be safely performed in practically every case including those in which there is tracheal obstruction Should crises occur pre operatively or post operatively good results may be achieved as they have in the past by the use of hypothermia to reduce the metabolic rate (Dundee and his colleagues 1953)

MYASTHENIA GRAVIS

This strange disease is of particular interest to anaesthetists not only because patients with this condition come to surgery but also because the muscle relaxants behave in an atypical fashion in these cases and indeed these abnormal responses have been utilized in diagnosing the condition

Churchill Davidson and Richardson in 1952 established that myasthenic patients are resistant to the action of normal doses of decamethonium and they also found that in mild cases larger doses of this drug would suddenly produce a prolonged paralysis in certain muscles and they postulated that these muscles

dosage based on urine analysis perhaps with occasional blood sugar checks erring on the side of too much sugar rather than risking hypoglycaemia

(6) Indwelling catheter usually required for major operations

(7) Rapid recovery of consciousness and minimal post operative stupor

(8) Absence if possible of post operative vomiting

Quick recovery, and minimal post operative vomiting may sometimes be conflicting requirements especially if the phenothiazine derivatives are used for the latter purpose and cautious dosage of these drugs is therefore indicated Close attention must also be given to dosage of post operative analgesics which should be selected for their minimal stimulating effect on the vomiting centre

If these principles are followed any modern general anaesthetic of the anaesthetist s choice may be employed, and there is seldom any necessity to use complicated major regional techniques with which the anaesthetist may be less familiar, though obviously the presence of diabetes mellitus may tip the scale in favour of local analgesia for many minor operations It must not be forgotten that the adrenaline which is so frequently required with major regional analgesias may raise the blood sugar as much as, or even more than a well given general anaesthetic Moreover, the heavy premedication required for such a procedure may well result in a longer period of stupor than after a general anaesthetic when relaxants are used

CORTICOSTEROID DEFICIENCY

The functions of the many adrenal and related pituitary hormones and their recently discovered synthetic analogues are described in another chapter They are important to the anaesthetist because a patient with absent or greatly impaired adrenal cortical function is unable to stand the stress of infection or trauma, and is likely to die within a few days of an operation unless adequate hormone replacement is provided The extent of the stress response initiated by the various anaesthetic drugs and techniques has not been fully determined but there seems little doubt that it is relatively small when compared with that of most operations (*Virtue and Helmrich 1956*) *The patients whose stress responses may be impaired* include (1) those for adrenalectomy for causes such as malignant disease or Cushing s syndrome (2) patients in whom adrenal function has been depressed or inhibited by prolonged treatment with cortisone, for example those with rheumatoid arthritis or lupus erythematosus (3) those with Addison s disease, (4) patients with acute adrenal insufficiency (5) those who are to undergo hypophysectomy pituitary stalk section or other forms of pituitary ablation, and (6) cases of *pan hypopituitarism or Simmond s disease This latter group is of mixed aetiology,* and varying severity and many of the patients first manifest symptoms shortly after parturition Sheehan (1939) estimated the incidence as 1 in 1,000 of the population, but only one fifth of these are severely affected and the author has not knowingly anaesthetized such a case

It matters little in essence whether the adrenal is removed, atrophied or deprived of effective pituitary control or if there are associated disturbances of other hormones causing for example diabetes mellitus or myxoedema which may be treated in the usual way All are in need of broadly similar management with regard to corticosteroid replacement The details of treatment will naturally vary but

the basic principle is to provide extra corticosteroid, usually cortisone to cover the stress of the operation, and more particularly the post operative period This must be given by injection immediately before operation and continued until absorption can again be guaranteed by mouth After a few days, the extra cortisone may be gradually reduced until a suitable maintenance dose is attained or resumed Patients on these high doses of cortisone have greatly reduced powers of resistance to infection, and prophylactic chemotherapy is usually indicated, but the greater risk is of a hypotensive crisis and strict attention must be paid to the details of fluid and electrolyte balance which is very unstable in these cases Nevertheless the blood pressure may fall to dangerously low levels in spite of apparently adequate supportive treatment It may be that the cortisone is not adequately absorbed or properly utilized and in these circumstances intravenous hydrocortisone has been found of great value This drug being in alcoholic solution must be considerably diluted before being injected, but this may be obviated by the use of a recently developed water soluble derivative, hydrocortisone hemi succinate Now that the value of hydrocortisone has become appreciated noradrenaline is less often required to control these hypotensive crises

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would be the next to be affected as the disease progressed Moreover, in advanced cases, normal doses of decamethonium were found, not infrequently, to produce a similar protracted paresis in the affected muscles The prolonged paralysis so *produced resembles that produced by a non depolarizing type of relaxant, such* as tubocurarine, in that it is reversible by neostigmine, but Churchill Davidson and Richardson (1953) have produced evidence that a neuromuscular block of this type is preceded by a transient depolarization block This dual action is characteristic of myasthenia, and a similar disturbance of motor endplate functions has been postulated in non myasthenics to explain some cases of prolonged action of other depolarizing drugs, such as suxamethonium (Argent, Dinnick and Hobbiger, 1955, Brennan, 1956)

The fact that all the muscles are resistant to decamethonium in the early stages of the disease provides considerable support for the view that myasthenia is a generalized disease and is not limited to the affected muscles

This is a more complicated concept than was originally appreciated, when the striking resemblance of the myasthenic state to the paralysis induced by curare led Bennett and Cash (1943) to suggest that this drug be used as a diagnostic test for myasthenia Support for this idea was given by reports of an unexpectedly prolonged response to curare in cases which were subsequently shown to be myasthenic In 1951, Dundee suggested that gallamine be used for this purpose, as this drug produced less subjective disturbance and less profound respiratory depression

In the diagnostic test using decamethonium described by Churchill Davidson and Richardson (1952), precise end points were obtained using electromyographic recordings from the hypothenar muscles In an endeavour to simplify this test the author dispensed with the electromyographic control and attempted to obtain an adequate end point by objective observation of muscle power, and by subjective responses Though well aware of the fallacies of such a method of evaluating the effects of relaxants and of its potential dangers it was felt that such a simple procedure was worth trying in cases in which the diagnosis was obscure Ten cases have been tested by this method Decamethonium tubocurarine and gallamine were injected at a standard rate on separate occasions on the same patient but the use of the latter drugs was abandoned after four cases since subjective distress came on early, and a clear end point was impossible to obtain Churchill Davidson (1955) has since pointed out that only those muscles which are clinically weak are hypersensitive to *d* tubocurarine the remainder responding normally

On the other hand a fairly clear evidence of sensitivity was obtained in five cases using decamethonium injected at the rate of approximately 0 25 milligram per minute after a loading dose of about 1 5 milligrams given slightly more rapidly Later follow up has confirmed the diagnosis of myasthenia in these five cases, of the remainder three were subsequently diagnosed as muscular dystrophy, one as multiple sclerosis and one probably hysterical Neostigmine, thiopentone and an anaesthetic machine were of course to hand and the latter combination was used twice once to relieve distress and once for subsequent muscle biopsy Neostigmine was used on all occasions after *d* tubocurarine and gallamine, and twice after decamethonium The fact that no serious difficulty was experienced was probably because no serious cases were accepted, and it is strongly felt that

such a test performed in this manner should be used only in early mild cases of intermittent paralysis where the diagnosis is seriously in doubt, and the therapeutic test with neostigmine has given equivocal results

When the myasthenic patient is presented for surgery, most often for thymectomy there is little time to observe these abnormal responses to relaxants Though both decamethonium and suxamethonium have been used to facilitate intubation, their use is not only unnecessary but they may seriously complicate the re establishment of respiration at the conclusion of the operation Profound anaesthesia is all too easily produced in these cases, with relatively small amounts of the usual agents, and if desired it is easy under any anaesthesia to take over control of the respiration Difficulty may be encountered with profuse secretion in the respiratory tract, but this can usually be overcome by frequent suction and additional doses of atropine

A small point of importance which may be overlooked in the preparation of severe myasthenics for thymectomy is to ensure that those patients who are receiving neostigmine or pyridostigmine by mouth are re established on those drugs by injection before operation, to ensure their effective absorption

Increased doses of neostigmine are often required in the post operative period, but excessive neostigmine may itself cause a muscular paralysis and occasionally this gives rise to great difficulty It is then necessary to stop all medication to clarify the diagnosis, and it is therefore essential that a mechanical respirator, though seldom needed be readily available The use of a tracheotomy and intermittent positive pressure has been advocated (Jorgenson and Therkelson, 1954) instead of a cabinet respirator in these crises, and Chang Harland and Graves (1957) have recently reported a case successfully treated by this method, which it seems reasonable to adopt if respiratory paralysis is prolonged more than a few hours Though such respiratory crises are fortunately rare post operative pulmonary collapse is more common than after other thoracotomies This is because the sternum splitting incision inhibits effective coughing and also because of the profuse secretions caused by neostigmine Atropine may of course be given but may complicate matters by making the sputum too viscid Close supervision and vigorous physiotherapy are therefore essential and bronchial toilet may have to be performed repeatedly

An interesting case has been described by Griffin, Nattrass and Pask (1956) who discuss many of the problems of management Their patient remained in myasthenic crisis for practically 44 days and had to be maintained for most of this time on mechanical ventilation with a tracheotomy Thymectomy was performed under nitrous oxide and pethidine anaesthesia on the 37th day, which operation ultimately resulted in considerable improvement In discussing the pathology of myasthenic crises Churchill Davidson and Richardson (1957) however, suggested that the improvement shown by this case was due to the resting of the motor end plates rather than to the thymectomy They further suggested that the end plates could be rested more effectively if *d* tubocurarine were administered in conjunction with sedation and mechanical respiration, and they describe a dramatic improvement in a case treated in this way where large doses of tubocurarine were given for 8 days

Most van Spijk and Lammers (1957) have reported the use of a similar regime in 4 cases but their results though encouraging were less dramatic However they only administered curare for 24 hours and unlike Churchill Davidson and

would be the next to be affected as the disease progressed Moreover in advanced cases, normal doses of decamethonium were found, not infrequently, to produce a similar protracted paresis in the affected muscles The prolonged paralysis so produced resembles that produced by a non depolarizing type of relaxant, such as tubocurarine in that it is reversible by neostigmine, but Churchill Davidson and Richardson (1953) have produced evidence that a neuromuscular block of this type is preceded by a transient depolarization block This dual action is characteristic of myasthenia and a similar disturbance of motor endplate functions has been postulated in non myasthenics to explain some cases of prolonged action of other depolarizing drugs, such as suxamethonium (Argent Dinnick and Hobbiger, 1955, Brennan, 1956)

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important consideration in the anaesthetist's assessment of the cardiac patient Although there are many new methods of analysing pulmonary function (D Silva 1956) they have yet to be proved to be of value in the pre operative assessment of patients for though no single test can evaluate all aspects of pulmonary function, yet the work of Miller, Wu and Johnson (1956) using the timed expiratory capacity, indicates the likely direction of future developments in this field

Thiopentone must be injected very slowly in order to avoid hypotension in patients with cardiac disease This applies particularly to cases of coronary insufficiency where the vicious circle of fall in blood pressure—poor coronary filling—myocardial hypoxia—weak contraction of the heart—fall in cardiac output with further fall in blood pressure is all too easily started The direct depressant effect of thiopentone on the myocardium may also help initiate this cycle A further reason for extremely slow injection is that the arm-brain circula tion time is often prolonged in cases of valvular incompetence or early congestive failure Maintenance of anaesthesia presents relatively minor hazards compared with the induction and recovery periods and even these hazards are reduced by the previous administration of oxygen for a few minutes Adequate premedication is necessary to lower oxygen consumption and to diminish the likelihood of adrenaline secretion which may cause ventricular fibrillation

If the above principles are observed there are very few cardiac patients who need be refused general anaesthesia and the only strong contra indication to elective surgery is a very recent coronary thrombosis where there may be a soft infarct in the myocardium Though diagnosis may be difficult and the electro cardiogram be misleading fatalities may occur if this condition be missed

Bellett (1956) discusses the problems of anaesthesia in coronary disease at length but it should not be forgotten that occult forms of the disease may not be diagnosable clinically (Blumgart, Schlesinger and Davis, 1940) That it is virtually impossible to forecast when a patient is going to get a coronary occlusion implies a risk that must be accepted, this also renders difficult the statistical assessment of the aetiological significance of anaesthesia and operation

The markedly hypertensive patient with a history of coronary occlusion and increasingly severe angina must however be regarded seriously Some authorities (Hayward 1956) recommend that quinidine 5 grains should be given three times a day for a few days before and after operation to this type of case, which is often associated with aortic stenosis and here hypertensive episodes are particularly to be avoided

Provided that pulmonary hypertension is not excessive, patients with other types of valvular heart disease may usually be anaesthetised without trouble, even where there is some mild congestive failure but this condition should be controlled as far as is possible before operation Opinions differ regarding pre operative digitalization but this is usually unnecessary for extrathoracic operations, except where specifically indicated as in congestive failure and auricular fibrillation

For operations inside the chest the situation is not comparable and the strain on the heart is usually greater Digitalization is then often indicated, and indeed at some thoracic centres all patients over 50 years old even without known cardiac disease receive digitalis pre operatively (Chin 1957)

Auricular fibrillation in a digitalized patient is of no significance, while of the other pre operative arrhythmias only gallop rhythm need cause concern

Richardson encountered a sensitivity to curare in 1 patient, who failed to benefit from the treatment

CARDIAC DISEASE

The recent dramatic progress in cardiac surgery has shown that many patients with severe heart disease even when congestive failure is present may safely be anaesthetized but this should not be allowed to lull the anaesthetist into a sense of false security when dealing with intercurrent heart disease in general surgical cases Although undoubtedly the risk for these patients has been overstressed in the past it must not be forgotten that cardiac patients for general surgery are usually older and therefore may have less myocardial reserve than those for elective cardiac surgery They differ from the cardiac surgery group in that there is not the immediate improvement in their circulation which results from a successful cardiac operation The not infrequently grave post operative condition of those patients in whom surgical relief to an impaired circulation has proved impossible is proof that even modern anaesthesia and surgery throw an appreciable strain on the severely diseased heart (Secher 1957)

Many attempts have been made to assess a patient s ability to withstand the cardiovascular strain of operation from the breath holding test of Sebrazes in 1902 (Mason 1956) to the ballistocardiogram (Wang and Howland 1956) but none has found widespread acceptance Although these tests are of interest and in some cases are a guide to the amount of hypoxia or hypercarbia that a conscious patient can withstand they give little information of value to the anaesthetist in his management of the case

The most serious hazard for the heart during anaesthesia is myocardial hypoxia which may be produced by poor coronary filling due to hypotension from any cause or by impaired oxygenation of the blood secondary to a disturbance of respiration The anaesthetist s pre operative assessment of severe cardiac patients is based largely on his estimate of any anticipated difficulty in preventing such incidents Can he guarantee an uninterrupted respiratory exchange and has the patient a sufficient volume of circulating blood to maintain his blood pressure at a reasonable level during spontaneous or controlled respiration?

The use of the relaxants and controlled respiration ensures uninterrupted respiration and avoids episodes of breath holding and coughing Marked broncho spasm or emphysema may however render controlled respiration impossible or dangerously inefficient and in these circumstances the use of a breathing machine which provides a negative pressure during expiration may often be of advantage

The operative period however is not necessarily the time of greatest stress indeed, with the lowered metabolism and rich oxygen atmosphere the condition of the cardiac patient is often temporarily improved

Of greater moment is the risk of a post operative atelectasis pneumonia or pulmonary embolus complications associated with pulmonary hypertension and which are likely to prove fatal when the heart is already diseased Although the site of operation is of paramount importance the presence of pre existing pulmonary disease such as emphysema or bronchitis makes the prognosis considerably worse and it is therefore essential that any chest infection is vigorously treated pre operatively

Thus it is respiratory rather than cardiac function which is often the more

particularly important in very ill patients and those with severe liver disease, for under these circumstances the ability to metabolize citrate rapidly is impaired

Firt and Hejhal (1957) have elucidated the mechanism of citrate intoxication, and the subject is fully reviewed in a leading article in the Lancet (1957b)

Polycythaemia

Polycythaemia is found as a compensatory mechanism in high altitude acclimatization, and in some heart diseases, notably in children with Fallot s tetralogy, where the intense cyanosis is partly due to this condition Specific treatment is not indicated, indeed, as the polycythaemia is compensatory, venesection would reduce the amount of available oxyhaemoglobin, which is already barely sufficient for the resting state, and such a loss would outweigh the benefit of lessened cardiac strain produced by thinning the blood A relative polycythaemia is also present in oligaemic shock

In adults who come to surgery with polycythaemia rubra, the situation is different The increased viscosity of the blood in this condition predisposes to thrombotic episodes and increases the strain on the myocardium Venesection is regularly prescribed for such patients, and should be part of the preparation for all operations in which blood loss is not anticipated This is normally sufficient, but dilution of the blood may be further encouraged by administration of intra venous glucose saline solution Early post operative ambulation is desirable but the anticoagulant drugs may usually be kept in reserve

Haemophilia

Haemophilia is the best known of a hereditary group of diseases in which the blood clotting mechanism is defective and of which the precise pathology is slowly becoming understood No case should be so labelled without full haemato logical investigation Although occurring in varying degrees of severity, it inevitably adds considerably to the hazards of surgery in any patient unfortunate enough to be so afflicted

The essential deficiency is of an 'anti haemophilic globulin" (A H G) which is normally closely associated with the fibrinogen fraction of the plasma proteins (Christmas disease (Biggs and her colleagues 1952) previously thought to be haemophilia, is due to a deficiency of a quite different factor normally present in the serum) Many attempts have been made to separate this substance and make it available for clinical use but with only limited success and fresh blood has been the most useful and readily available therapeutic source Natural A H G obtained in this way deteriorates rapidly so that the blood must be given within 48 hours of being drawn and preferably sooner (Dacie 1952)

Although one litre of fresh blood may reduce the clotting time to normal in a favourable case in a remission it is usually difficult to achieve this end without overloading the circulation in a patient who is not bleeding On the other hand when bleeding occurs there is a further complication in that A H G is not an enzyme or accelerating factor but is actually used up in the clotting process Very large quantities of blood are therefore required for even minor operations in spite of using ancillary measures such as topical applications of thrombin or Russell Viper venom In an attempt to make larger quantities of A H G available

Arrhythmias due to reflex stimuli or anaesthetic agents are seldom serious in a well oxygenated heart when the blood *p*H is not disturbed, therefore irregularities of the pulse arising during anaesthesia should always arouse the suspicion of myocardial hypoxia, and an increased supply of oxygen with an augmented respiratory exchange will nearly always improve the rhythm and volume of the pulse The author has never felt the need for procaine amide or other drugs to control cardiac irritability during extrathoracic operations

Although Hayward (1956) and Beard and Goodwin (1956) have recently discussed the assessment of the cardiac patient for surgery there is little satisfactory statistical information available on the risks involved for such a patient undergoing routine extra thoracic surgery under modern anaesthesia

Of paramount importance ar the skill and experience of the anaesthetist and surgeon in avoiding hypoxia and preventing post operative complications, and this fundamental axiom does not always lend itself to mathematical analysis

BLOOD DISORDERS

Anaemia

The anaesthetist is more concerned with the severity than with the nature of an anaemia and although many of these patients can be improved by appropriate medical treatment, there is frequently insufficient time for such therapy to become effective in patients presented for surgery and resort must be made to blood transfusion It is not possible to define a critical level of haemoglobin below which operation is inadvisable much will depend on the clinical assessment and the nature of the proposed operation and on the availability of suitable blood

If transfusion is considered advisable the rate at which it can be given depends on the patient s blood volume which is frequently increased in chronic anaemias unassociated with recent severe haemorrhage In these cases transfusion must not be hurried and packed cells are often preferable to whole blood A bolder policy may be adopted in preparing for operation patients with malignant disease especially if they are dehydrated or undernourished for these cases frequently have a lowered blood volume as well as a low haemoglobin and they are consequently much less easily overtransfused

Though not always practicable a pre operative blood transfusion should preferably be given more than 24 hours before surgery for even if antihistamines or sedatives are given minor reactions may yet occur and these tend to deprive the patient of much needed rest moreover there may be increased bleeding during the operation if it is undertaken too soon after a mild overloading of the circulation

Although it has been argued that transfusion may restart the bleeding in a patient with peptic ulcer once the decision to operate has been taken the anaesthetist would be advised to give blood generously and rapidly Emergency gastrectomy for bleeding ulcer is becoming a common procedure and the author has yet to see harm come from overtransfusion of blood in these sometimes severely ill patients provided that the risk of citrate intoxication is borne in mind This risk may be considerably reduced by the simultaneous administration (into a separate vein) of 10 millilitres of 10 per cent calcium gluconate per 500 millilitres of blood, whenever rapid and massive transfusions are given This treatment is

clinical variation, and there seems little doubt that the standard modern anaesthetic sequence of minimal thiopentone–nitrous oxide–oxygen–tubocurarine–pethidine, does not materially depress hepatic function, though common sense advises caution in the dosage of all premedicant drugs This is confirmed by experience in patients with obstructive jaundice, who invariably seem to do well in the absence of surgical or other complications

Patients with chemotoxic jaundice seldom come to surgery, but in two instances where this was due to chlorpromazine recovery did not appear to be impaired by general anaesthesia and laparotomy Acute infective hepatitis, however, must be regarded more seriously and since it tends to relapse and its course is un predictable is usually considered a contra indication to elective operations

The only case of post operative hepatic failure in the author s personal experience followed an exploration of the common bile duct mistakenly undertaken to relieve jaundice due to infective hepatitis but recovery fortunately followed treatment with intravenous glucose Insulin and amino acids such as methionine are not only unnecessary but may even be dangerous in the treatment of liver failure (Sherlock 1955) a condition likely to be encountered by the anaesthetist only in cases operated on for the relief of portal hypertension

RENAL DISEASE

All forms of renal disease may be considered together, and the anaesthetist need only consider the severity of any resultant uraemia This term covers a more complicated electrolytic disturbance than just a raised blood urea and as is well known such a state may progress through stupor to coma and death Doses of the non volatile narcotics and analgesics especially thiopentone, must be kept minimal The post operative sleep after the latter drug is markedly prolonged in proportion to the severity of the uraemia (Dundee, 1956)

Before major surgery every effort must be made to correct dehydration and electrolyte imbalance, and to provide urinary drainage For this latter purpose modern general anaesthesia need not be refused provided minimal thiopentone is used and in severe uraemia as little as 50 milligrams may be sufficient

Cyclopropane or nitrous oxide are the most useful agents and of the relaxants suxamethonium or tubocurarine need not be withheld if used with discretion Gallamine and decamethonium should be avoided as they are excreted probably entirely in the urine

In the past decapsulation of the kidney for the treatment of anuria has been performed without appreciable deterioration in the patient s condition which could be attributed to the general anaesthesia employed High spinal analgesia has also been recommended as the sole therapeutic measure but both these dramatic approaches to the treatment of anuria have been largely superseded by the conservative dietary regime, or by dialysis

PORPHYRIA

This rare disease of unknown aetiology is associated with skin pigmentation showing photosensitivity attacks of abdominal pain and progressive lower motor neurone paralysis In its later stages or after abdominal symptoms a characteristic red urine is secreted—porphyrinuria Unfortunately this dramatic

Bidwell (1955) has prepared a concentrate from bovine and other animal blood These products have the disadvantage of sensitization of the recipient to foreign protein and it is possible that they become less effective after repeated doses Nevertheless Fraenkel and Honey (1955) found them of value in a case which even so required vast quantities of blood before the patient was out of danger

More recently Kekwick and Wolf (1957) have prepared a promising extract of A H G from human blood of which 100 millilitres are equivalent to a litre of fresh plasma Though less concentrated than the bovine extract the disadvantages of the latter are avoided these authors have described its successful use in 6 cases

This new product marks a great advance in the treatment of the haemophiliac nevertheless it would be unwise to embark on an operation in such a patient without the full resources of a haematological laboratory and an ample supply of blood In the words of Dacie Operations have been performed successfully on haemophiliacs but before the patient is on his feet again the surgeon usually wishes that he had never operated Nevertheless, the number of cases who have successfully undergone surgery is steadily growing and these have recently been reviewed in a leading article in the Lancet (1957 a)

HEPATIC DISEASE

The bibliography on anaesthetics and liver function is vast and conflicting for example Waters (1951) in an extensive investigation and using a battery of tests found remarkably little hepatic disorder following anaesthesia On the other hand Dundee (1956) concluded that thiopentone in doses over 750 milligrams produced detectable dysfunction in an appreciable proportion of cases All that is beyond dispute is that if hypoxia occurs during anaesthesia it certainly may result in liver damage

The liver possesses vast functional reserves, and even when severely damaged the extent of such disturbance cannot easily be assessed by the many function tests which have been devised and all these investigations are of little value in assessing the probable effect of anaesthesia on an already diseased liver The author has anaesthetized a considerable number of patients with severe liver disease who were subjected to peritoneoscopy in an attempt to clarify the diagnosis and he has not found it possible in these cases (chiefly of cirrhosis or malignant disease) to correlate the response to anaesthetic agents with the liver function tests Dundee and Gray (1953) have described a resistance to *d* tubocurarine in the presence of impaired liver function this has been confirmed by the author on several occasions and by Haselhuhn (1957) but is by no means an invariable finding This discrepancy is presumably explained by differences in the serum cholinesterase level which may be depressed by many causes (Wielhorski and his colleagues 1956) but which is not consistently low in liver disease (Sherlock, 1955)

It is well known that the effects of morphine pethidine and other narcotics may be markedly prolonged in patients with a damaged liver but here again the response is unpredictable from function tests and often also from the clinical condition Many patients with inoperable carcinoma with gross involvement of the liver have been anaesthetized but hepatic failure is an extremely unusual sequel

Haselhuhn (1957) considered that the very slight reduction in thiopentone consumption noted in his cases with advanced liver disease was within the range of

REFERENCES

Biggs Rosemary Douglas A G MacFarlane R G Bacoie G V and Pitney W R (1952) *Brit med J* 2 1378
Blumgart H L Schlesinger M J and Davis D (1940) *Amer Heart J* 19 1
Brennan H G (1956) *Brit J Anaesth* 28 159
Chang J Harland J H and Graves H B (1957) *Canad Anaesth Soc J* 4 13
Chin E F (1957) *Post Grad med J* 33 612
Churchill Davidson H C (1955) *Proc R Soc Med* 48 621
— and Richardson A T (1952) *Ibid* 45 179
— — (1953) *J Physiol* 122 252
— — (1957) *Lancet* 1 1221
Dacie J V (1952) *Brit med J* 2 1408
Davies M H and Paley R G (1957) *Brit med J* 1 502
de Mowbray R R (1957) *Post Grad med J* 33 632
D Silva J L (1956) *Brit J Anaesth* 28 536
Dundee J W (1951) *Brit J Anaesth* 23 39
— (1956) *Thiopentone* Edinburgh Livingstone
— (1957) *Brit J Anaesth* 29 166
— and Gray T C (1953) *Lancet* 2 16
— Gray T C Mesham P R and Scott W E B (1953) *Brit med J* 2 1244
Edwards G Morton H J V Pask E A and Wylie W D (1956) *Anaesthesia* 11 194
Ellis G (1955) *Anaesthesia* 10 78
Firt P and Hejhal L (1957) *Lancet* 2 1132
Fraenkel G J and Honey G E (1955) *Lancet* 2 1117
Griffin S G Nattrass F G and Pask E A (1956) *Lancet* 2 704
Griffiths J A (1953) *Quart J Med* 88 405
Harris T A B (1951) *The Mode of Action of Anaesthetic Drugs* Edinburgh Livingstone
Haselhuhn D H (1957) *Curr Res Anesth* 36 73
Hayward G W (1956) *Post Grad med J* 32 104
J Amer med Ass (1937) Queries and Minor Notes 109 1218
Jorgenson J B and Therkelson F R (1954) *Acta chir scand* 107 414
Joseph J M (1952) *J Amer med Ass*, 149 1196
Kekwick R A and Wolf P (1957) *Lancet* 1 647
King R C (1957) *Anaesthesia* 12 30
La Salvia L A and Steffan E A (1950) *Amer J Obstet Gynec* 59 1075
Lancet (1953) 2 147
— (1957a) 2 376
— (1957b) 2 1152
Livingstone H Heidrick F Holicky I and Dack G M (1941) *Surgery* 9 433
Magath T B (1938) *Curr Res Anesth* 17 215
Mason S A (1956) *Brit med J* 2 766
McDonald W L J Welch H J and Keet J E (1955) *Anesthesiology* 16 206
Miller W F Wu N and Johnson R L (1956) *Anesthesiology* 17 480
Minnitt R J (1933) *Proc R Soc Med* 26 347
Most van Spijk D v d and Lammers W (1957) *Lancet* 2 94
Osborn R A (1957) *Brit med J* 1 501
Palmer K N V and Sellick B A (1952) *Lancet* 1 354
— — (1953) *Ibid* 1 164
Secher O (1957) *Proc R Soc Med* 50 983
Sheehan H L (1939) *Quart J Med* 32 277
Sherlock S (1955) *Diseases of the Liver and Biliary System* Oxford Blackwell
Smith A C (1957) Personal communication
Virtue R W and Helmrich M L (1956) *Proc R Soc Med* 49 492
Wang M D and Howland W S (1956) *Anesthesiology* 17 578
Waters R M (1931) *Calif West Med* 35 342
— (1951) *Chloroform* Madison University of Wisconsin Press
Wielhorski W A Dubeau M and Riopel P (1956) *Canad Anaesth Soc J* 3 31
Wynn V (1954) *Lancet* 2 575
Ziegler C and Jacoby J (1956) *Curr Res Anesth* 35 441

sign is seldom manifest in the latent stages of the disease, which is often not diagnosed until it has been exacerbated by drugs such as sulphonamide or, more particularly the barbiturates Dundee (1956) has reviewed this subject, and shows clearly that thiopentone is particularly harmful, and reported several cases in which the resultant paralysis progressed to a fatal outcome It would appear that this drug is absolutely contra indicated in this disease one of the very rare instances where such a dogmatic remark may be made about an anaesthetic agent in common use

GERIATRICS

An old patient s physical condition is best assessed by his functional state and the clinical findings, neither of these bears any relationship to numerical age However many old people are undernourished and have a vitamin deficiency They profit from a period of rest and feeding before operation and as they adapt slowly to change it is a kindness not to rush them into operation This policy allows adequate time to treat any intercurrent disease

Early post operative ambulation is particularly important and is made easier by the fact that many old people instinctively realize this Not infrequently they have a high pain threshold and need relatively small amounts of analgesics

Mental confusion accompanies most illnesses in the aged, and this is exaggerated by narcotics Careful supervision and minimal dosage are the only safeguards and one must beware of giving further or different hypnotics in an attempt to control restlessness which itself may be due to drugs Bedford (1955) has drawn attention to the frequency of mental changes following operation in the aged, and there is no doubt that the margin of safety is reduced in these patients, many of whom are hypertensive or have had episodes of cerebral thrombosis There seems little doubt that most of the cases he described were secondary to episodes of hypoxia or hypotension and the latter state must never be allowed to occur inadvertently still less intentionally Skilled anaesthesia, cautious dosage of analgesics and, above all, early and adequate blood transfusion are essential

There is a common belief that it is dangerous to transfuse old people and cardiac patients Danger lies only in rapid transfusion and it is therefore particularly important that blood should be given early but slowly in these cases so that the need for rapid administration should not arise The use of pressor drugs should seldom be necessary but they should not be withheld

With adequate preparation and care taken to prevent hypotension, there are few patients who need be denied the benefit of surgery, such as prostatectomy in men and the relief of prolapse and stress incontinence in women These may not come under Bedford s category of unequivocally necessary , but only when recent mental deterioration has appeared need a circumspect approach to surgery be advocated for such a change frequently presages the final dissolution

REFERENCES

Argent D E Dinnick O P and Hobbiger F (1955) *Brit J Anaesth* 27 24

Beard A J W and Goodwin J I (1956) *Brit J Anaesth* 28 557

Bedford P D (1955) *Lancet* 2 259

Bellet S (1956) *Anesthesiology* 17 391

Bennett A E and Cash P T (1943) *Arch Neurol Psychiat Chicago* 49 537

Bidwell E (1955) *Brit J Haematol* 1 35

to obstruction is likely to recur, or to continue, the trachea must be intubated with a cuffed tube Inhalation of the obstructing agent may have occurred, in which case bronchoscopy must precede, or catheter suction follow intubation Such a state of affairs may be encountered after a severe fracture of the maxilla, which can give rise to considerable haemorrhage If the patient is vomiting a wide bore tube should be passed down the oesophagus and stomach drainage instituted

Laryngeal obstruction

Obstruction at the level of the larynx will necessitate careful and gentle intubation but on occasion it may be relieved only by tracheotomy

Bronchial obstruction

Foreign bodies aspirated material such as water, food, vomitus or blood or bronchopulmonary secretions may block the lower air passages Bronchoscopy and suction with postural drainage and energetic physiotherapy will be the measures demanded

Aetiology

Among the obstructive conditions which may be encountered are new growths of the pharynx larynx thyroid, or of the structures within the thorax haemorrhage aspiration of foreign bodies including food and fluids inflammatory conditions especially those affecting the floor of the mouth and the laryngo pharynx fractures of maxilla or mandible bilateral adductor paralysis of the vocal cords injury to the lungs and bronchi including tension pneumothorax One interesting and possibly hopeful therapy is the bronchoscopic treatment of status asthmaticus Sometimes the bronchospasm can be dramatically relieved by the local application of a few millilitres of lignocaine The successful outcome of this manoeuvre is most rewarding in an unconscious patient with a dwindling tidal volume, tracheal tug and commencing peripheral vascular failure

Depression of the respiratory centre

The activity of the respiratory centre situated in the pons and medulla oblongata, may be depressed by drugs or by products of abnormal metabolism, or may be affected by injury or vascular catastrophe Depression of the respiratory centre will if severe or prolonged reduce ventilation below the level of minimal efficiency The lungs of a patient in coma are vulnerable to the hazard of atelectasis from aspiration or accumulated secretion and even small areas of collapse added to a state in which the tidal volume is already diminished by central depression may precipitate an anoxic crisis Head injuries or the sequelae of cranial surgery and of some neurological diseases poisoning by such drugs as barbiturates or opiates, intoxications such as occur in diabetes nephritis or eclampsia, carbon dioxide coma in chronic bronchitis and emphysema, these are but some of the conditions for which the anaesthetist may be called upon to restore normal physiological equilibrium by re establishing respiratory efficiency After initial clearance of the airway artificial respiration must be carried on for so long as the respiratory centre is functioning inadequately This may necessitate the maintenance of mechanical ventilation for days on end and will present technical problems which will challenge the ingenuity and tax the endurance of the most highly organized anaesthetic department

CHAPTER 18

THE ROLE OF THE ANAESTHETIST IN DISORDERS OF THE RESPIRATORY SYSTEM

PATRICK SHACKLETON

TECHNIQUES learned and practised in the operating theatre during the last two decades have fitted the anaesthetist to take his place as a respiratory physiologist and as an applied pharmacologist in the therapeutic team Here his advice and assistance are becoming more and more frequently sought His most valuable contribution will probably be made in the treatment of patients in whom the normal respiratory function is threatened or gravely impaired

IMPAIRED RESPIRATORY FUNCTION

Classification

The conditions leading to impairment of respiratory function may be classified as follows

(1) Obstruction of the air passages somewhere between the atmosphere and the alveolar capillary barrier

(2) The effect upon the respiratory centre in the brain of depression or damage

(3) Interruption of the paths of transmission of nervous impulses between the brain and the muscles of respiration

(4) Conditions affecting the muscles of respiration themselves or their attachments

In practice the treatment of all these conditions resolves into two problems the establishment and maintenance of an adequate airway and the amplifying of inadequate respiration or respiratory control during apnoea

Respiratory obstruction

Respiratory obstruction may be acute or may develop slowly It may affect either of the two main functions of respiration oxygenation and the elimination of carbon dioxide equally or one more than the other It may be intrinsic as in conditions in which a growth a foreign body or secretions block the lumen of the passage or extrinsic as where pressure from a growth or haemorrhage inflammation or tension pneumothorax constricts the airway

Pharyngeal obstruction

Obstruction of the airway may occur in the pharynx by haemorrhage or vomitus and laryngoscopy and suction may be all that are needed If the condition leading

Anoxia will increase capillary permeability and, with a low intra alveolar pressure may lead to pulmonary oedema Full ventilation with I P P R will both start the reversal of the acidosis and may prevent or reverse the pulmonary oedema Tracheotomy serves as a convenient and efficient port for suction toilet which must be continued until the acute stage of the infection is controlled by antibiotic therapy

Respiratory pumps

The relative merits of the different types of respiratory pump have been very fully discussed (Mushin and Rendell Baker, 1954) In the chronic bronchitic with emphysema who develops acute respiratory insufficiency a machine which can produce a sub atmospheric pressure at the end of the expiratory phase carries an advantage and imposes less upset of circulatory dynamics The great dis advantage of I P P R , life saving though it may be is its direct reversal of the normal intrathoracic pressure pattern with resulting impediment of the venous return to the heart

Resuscitation of the newborn (see also p 217)

Resuscitation of the newborn often falls within the province of the anaesthetist The decision when to employ more active treatment than the traditional passes often accorded to the apnoeic baby may be a difficult one The slowing heart rate of anoxia is probably as good an indication as any that active assistance is urgently required, although a myocardium which is feeling anoxic strain to the extent of exhibiting a bradycardia of the order of 80 or 70 beats a minute may indicate cortical damage of an extent which bodes ill for the child s future A rate of 100 beats per minute which is continuing to fall after a further minute of observa tion should demand more active interference All infants should be placed after birth on to an inclined board or table top in the head down position, and not put immediately into a cot or oxygen box Liquor will then drain naturally from the air passages and resuscitative measures simple or more elaborate, may be easily performed If with simple measures such as cleaning the pharynx of liquor and amniotic debris, and the passing of a fine oxygen catheter through the posterior nasopharynx (which often elicits the sneeze reflex and starts rhythmical respira tions) a respiratory rhythm is still not established intragastric oxygen may be commenced A more effective measure, though requiring skill and practice, is tracheal intubation followed by very carefully controlled intermittent positive pressure (Blaikley, 1956) An oxygen flow of one litre per minute into the side limb of a T piece connected to the endotracheal tube and finger blocking of the other limb for one second in every three may be applied safely until spontaneous respiration commences The object of this manoeuvre is not immediately to inflate the lungs but to raise rhythmically the intratracheal and intrabronchial pressure, so acting upon the stretch receptors in the pulmonary interstitial tissue as to actuate the Hering Breuer reflex Passage of oxygen into the blood stream *via* the tracheal and bronchial mucous membranes also occurs A baby whose respiratory centre is silent because of depression from morphine or pethidine given to the mother late in labour may be released into respiratory activity by the timely use of an antagonist such as nalorphine

Management of the unconscious patient

The management of the unconscious patient has been described by Mushin (1955). Nevertheless it is surprising how the two essential principles of establishing a clear airway and instituting and maintaining adequate ventilation are often neglected. These two measures are vital in the treatment of any respiratory emergency and until they are taken the patient's life is in immediate danger. *The aims are to ensure the maximum oxygenation of the patient's blood and to* remove carbon dioxide from his circulation. These two functions of respiration may not be achieved unless the basic principles of the physiology of respiration are remembered. The administration of oxygen may convert a blue patient to a pinker colour, but unless the tidal volume as well as the minute volume of respiration are adequate carbon dioxide will accumulate in the body. A small tidal volume even with a high minute volume may be inadequate as the ratio of tidal volume to dead space may be too small. The immediate treatment therefore of the apnoeic patient or one whose respiration is inadequate is to establish a clear airway and to ventilate the lungs with an air or oxygen flow of 8–10 litres a minute. The diagnosis of the condition causing respiratory insufficiency can then be made in an atmosphere more conducive to clear thinking.

If the condition is one in which central impairment of respiration is likely to be of brief duration ventilation may be maintained by "bag squeezing", but if maintenance is going to occupy hours or even days or weeks a more thorough organization must be developed. Tracheal intubation and ventilation by some form of respiratory pump must be employed. Should the way ahead appear long tracheotomy should be performed and intermittent positive pressure respiration carried out through the cuffed tube inserted through the tracheotomy. One practical point is of importance here. The tracheotomy should be performed as high as possible, the operator dividing the thyroid isthmus and cutting a diamond shaped window in the trachea. Too low or too long a slit incision in the trachea may allow the tube to slide down on to the carina or into one of the main bronchi. Intermittent positive pressure respiration (I P P R) is most easily carried out in a totally apnoeic patient, it is not so satisfactory in those cases in which the patient makes inadequate attempts at spontaneous respiration. In these circumstances a machine triggered by the patient's own respiratory effort will be of great help in producing assisted respiration. In the absence of such a machine it may be necessary to abolish the ineffective respiratory movements by a muscle relaxant and assume full control of ventilation.

Superimposed acute respiratory infections

Patients with acute respiratory infections superimposed on chronic lung disease are sometimes admitted to hospital in a grave state of uncompensated respiratory acidosis (Biorneboe and his colleagues 1955). They are dyspnoeic and cyanotic and are often given oxygen therapy whereupon they may pass from dyspnoea to apnoea. The reason for this phenomenon which may trap the unwary is that when a respiratory centre tuned to a high carbon dioxide concentration is exposed to a sudden increase in oxygen concentration its activity is reduced still further because of removal of the hypoxic drive from the peripheral chemoceptors

relaxants Tracheotomy is essential in cases of tetanus so treated and control by muscle paralysis and ventilation may have to be maintained for many days Management as in all respiratory cases is essentially a matter of team work, and the nursing problems are severe in the extreme During the active control of the tetanic spasms it seems reasonable on humanitarian grounds as well as to limit the trigger effect of external stimuli to keep the patient centrally sedated Light nitrous oxide oxygen anaesthesia was employed by some until Lassen and his colleagues (1956) cast doubts upon the harmlessness of prolonged anaesthesia with this agent Some patients with very severe tetanus who from the incubation period stage of onset and severity of symptoms might have been expected to die, have been successfully treated with tracheotomy and intubation muscle relaxants and I P P R The use of chlorpromazine seems to offer further help particularly in those cases of tetanus where hyperpyrexia is a feature and more especially when this appears to be associated with involvement of the brainstem

The convulsions of strychnine poisoning can be treated in the same way as tetanus Indeed the whole technique is available for any and every case of convulsion or apnoea whether due to central or more peripheral causes

Myasthenia gravis

The acute respiratory crisis of myasthenia gravis presents some interesting problems (Griffin Nattrass and Pask 1956) Quite apart from the maintenance of ventilation which should be along the lines already indicated a pharmacological conundrum may be posed Often very large doses of neostigmine have been given prior to the crisis becoming acute The possibility arises that there has been inadequate elimination of the drug and that a concentration has been built up sufficient of itself to produce a degree of neuromuscular blockade Thymectomy may be performed at this stage but it is essential to proceed back to spontaneous respiration slowly and carefully continuing the respiratory control for at least a week after the last dose of neostigmine

When it is suspected that this may be the case it is advisable to stop all therapy and depend on pulmonary ventilation for 24 hours or so Not infrequently some spontaneous respiration will recommence and from then it is easy to observe the effect of doses of neostigmine pyridostigmine or perhaps because of its transient action edrophonium (Tensilon) which is the most useful drug for this type of therapeutic test

Head injuries

Head injuries sometimes present as respiratory problems Inefficient respiration or complete apnoea may be the result of direct injury to the brainstem or to a generalized rise in intracranial pressure Often these patients can be kept alive for days without any response from the respiratory centre which has been damaged beyond repair A sort of nightmare state is built up in which a patient can turn into a heart lung preparation where coronary and pulmonary circulation are mechanically maintained without a flicker from any other part of the body It is disturbing to record a normal complex on the electrocardiogram in a patient who one suspects is dead! *Nevertheless* such pessimism must be resisted and the reward of an unexpected recovery confidently awaited

Interruption of nervous impulses

Poliomyelitis

The classic example of respiratory inefficiency due to interruption of the nervous impulses occurs in anterior poliomyelitis It is into this field of therapeutics that the anaesthetist has been called most urgently and where he has made perhaps his most spectacular contribution When poliomyelitis affects the higher part of the cervical cord, ventilation will be diminished and suboxygenation and carbon dioxide retention occur Such cases may best be relieved by treatment in a box respirator but if the brain stem is involved as well as the cervical cord more than ventilation will be affected The protective function of the glottis will be impaired, the action of swallowing disorganized and the air passages will become vulnerable to the aspiration of secretions or of food The measures adopted by Lassen (1953) and Ibsen (1954) in the 1953 epidemic in Copenhagen brought the everyday techniques of the anaesthetist to the rescue of these unhappy people To the management of bronchial secretions by suction and physiotherapy was added the use of intermittent positive pressure respiration applied through a cuffed endo tracheal tube inserted through a tracheotomy opening By this technique the Danish workers reduced the mortality of these cases of spinobulbar poliomyelitis from some 80 per cent to 30 per cent In many countries it is now the custom to gather such patients into special units where they are treated by a team consisting usually of a physician, an anaesthetist and an ear nose and throat surgeon assisted by a biochemist and a physiotherapist Such hospitals have a mobile service to safeguard the patient during the journey from home to the unit Endo tracheal intubation may be necessary before undertaking the journey and a means of ventilation either by hand bellows or bag or by pump should be available in the ambulance or aeroplane, together with adequate suction

The same techniques of maintaining adequate ventilation may be applied successfully in the apnoeic crises of myasthenia gravis of polyneuritis of some of the rare myopathies such as polymyositis, and in injuries to the cervical spinal cord

Tetanus

Tetanus kills by asphyxia by exhaustion or more frequently by pulmonary complications due either to infection or to aspiration of food fluids or pharyngeal secretions Modern treatment (Woolmer and Cotes 1952 Shackleton 1954 Ablett 1956) aims at limiting or stopping the spasms altogether, maintaining adequate ventilation and treating the pulmonary condition by antibiotics and physiotherapy Control of muscle spasms may be achieved by central sedation or such treatment may be combined with an attempt to reduce muscle tone with the aid of mephenesin However in some cases it may be necessary to produce complete muscle paralysis with drugs of the muscle relaxant groups in which case the muscles of respiration will share in the paralysis and controlled ventilation will become necessary Almost all the known muscle relaxants have been used in this conversion of severe tetanus to a state analogous to that of reversible spino bulbar poliomyelitis The advantage of the short acting relaxants given by intra venous drip appears to be flexibility and minute to minute control On the other hand, some workers claim greater safety and effectiveness with the longer acting

often be replaced by intragastric therapy Routine biochemistry can be performed at arranged times Physiotherapy and tracheobronchial suction toilet become, with practice, less and less of an ordeal for the staff and patient

SPECIALIST SERVICES

In certain special hospitals or units the scope of the anaesthetist s responsibilities extends into fields of even wider application In some thoracic units the important business of assessment of pulmonary function falls to the anaesthetist s lot and there is wide scope for clinical investigation both before and after surgery In plastic surgery units to which patients with burns gravitate in these days, the anaesthetist has a useful part to play in the general management of these far from easy cases The treatment of burn shock', with the hour to hour adjustment in intravenous infusion and transfusion and the problems of maintaining efficient tissue oxygenation, especially difficult in children, are of absorbing interest and vital importance

REFERENCES

Ablett J Y L (1956) *Brit J Anaesth* 28 258

Biorneboe M Ibsen B Astrup P Everberg G Harvald B Sottrup T Thaysen E H and Thorshauge C (1955) *Lancet* 2 901

Blaikley J B (1956) *Proc R Soc Med* 49 603

Crampton Smith A Spalding J M K and Russell W R (1954) *Lancet* 1 939

Griffin S G Nattrass F J and Pask E A (1956) *Lancet* 2 704

Ibsen B (1954) *Proc R Soc Med* 47 72

Lassen H C A (1953) *Lancet* 1 37

— Henrikson E Neukirch F and Kristensen H S (1956) *Lancet* 1 527

Mushin W W (1955) *Brit med J* 1 1116

— and Rendell Baker L (1954) *Brit J Anaesth* 26 131

Shackleton P (1954) *Lancet* 2 155

Woolmer R (1956) *Post Grad med J* 31 463

— and Cotes J E (1952) *Lancet* 2 808

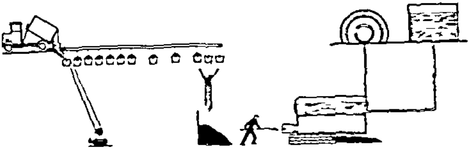
Respiratory muscle disorders

Injury to the thorax and to the accessory muscles of respiration may, by pain or by the mechanical effect of "flail chest" or tension pneumothorax, produce a *state of respiratory insufficiency*. *Where pain alone is the cause, adequate analgesia* by local or central medication may suffice. In the disruption of the mechanics of respiration in flail chest I.P.P.R. will eliminate paradoxical respiration and restore normal respiratory dynamics.

MANAGEMENT OF PATIENTS IN APNOEA

The general management of these apnoeic cases demands great care and thought. They bristle with technical and physiological problems. Pulmonary oedema is always imminent whether is a result of the disease process itself or precipitated by the disturbance of vascular respiratory dynamics as a result of the treatment. The maintenance of fluid balance and of electrolyte control may be most difficult, but will be rendered so much more easy if intravenous replacement can be avoided. Therefore the passage of a reasonable sized stomach tube should be a *sine qua non* of the technique, so that nutrition and body chemistry can be maintained in a natural manner.

The problems arising out of prolonged artificial ventilation are numerous (Woolmer, 1956). Ventilation may become difficult due to inadequate removal of secretions or to collapse of one or more pulmonary segments. Ventilation which appears adequate may, an hour later, be apparently not fulfilling its function. Acidosis or alkalosis may be present, but which of these states exists may not at once be easy to decide. Such a patient may pass from acidotic coma, due to inadequate ventilation, to alkalotic unconsciousness due to hyperventilation with remarkable ease. Acidosis may arise insidiously as a result of diminished ventilation due perhaps to undetected obstruction from secretions, bronchospasm, anoxia from any cause, or to the superimposition of renal acidosis. The consequence is medullary depression and a breakdown of the renal compensatory mechanism. Alkalosis, on the other hand, will, if severe or prolonged, upset the haemoglobin dissociation curve and so limit tissue oxygen uptake. In extreme cases tetany may occur or renal calculi may be laid down, and so repeated records must be made of the serum and urine *p*H, total and combined carbon dioxide and of serum electrolytes. Blood pressure and pulse charts and fluid balance records must be accurately kept. The electrocardiogram and the electroencephalogram may be of help. Death in all cases is ultimately anoxic, but in the type of case discussed here primarily so. Although in Great Britain it is usually only the poliomyelitis cases which are concentrated in special centres, it is becoming more frequent, especially in Scandinavia, to establish special "respiratory wards". Into these wards, which in one case at least (in Sweden) are in the charge of the anaesthetic department, are transferred those cases presenting a problem in the establishment and maintenance of adequate ventilation. There is much to be said for collecting such cases together (Crampton Smith, Spalding and Russell, 1954) for the successful management of apnoeic patients relies essentially on team work and on skilled nursing. Every case needs "specialling" and the minute to minute management becomes a nursing problem. Techniques should be standardized as much as possible and complicated measures avoided. Intravenous therapy can



ANOXIC	STAGNANT	ANAEMIC	HISTOTOXIC: EXTRACELLULAR	HISTOTOXIC: PERICELLULAR	HISTOTOXIC: METABOLITE	HISTOTOXIC: SUBSTRATE
High altitudes	Shock	Anaemia	Hypnotics	Ether	Carbon dioxide	Hypoglycaemia
Asphyxia	Cardiac failure	Carbon monoxide	Barbiturates	Chloroform	Uraemia	
Drowning			Opiates	Cyclopropane		
Lung diseases			Cyanide	Trichloroethylene		
Pulmonary oedema						
Nitrous oxide				*Nitrous oxide*		
	Cerebral ischaemia				Cerebral ischaemia	Cerebral ischaemia

In this diagram coal representing oxygen is transported to a furnace representing a cell The atmosphere is portrayed by the lorry and the energy produced in the cell by the turbine The circulation and heart are shown by the bucket conveyor system and motor Tissue respiration is represented both by the stoker (extracellular) and the furnace door (pericellular) The cell substrate is depicted by the water in the boiler and the end products of metabolism are represented by the ashes from the furnace The transportation of coal may fail at any point and several minor defects at *different* stages will have a major effect upon the steam pressure Clinically more than one type of anoxia often occurs at the same time For example in acute cerebral ischaemia the brain will suffer from stagnant anoxia due to failure of oxygenated blood to reach the head also there will be no substrate for the brain to metabolize because of the absent circulation nor can the metabolites be removed In cerebral ischaemia due to cardiac arrest occurring during surgery there is the added factor of the anaesthetic agent

FIG 27 —Analogy of coal transportation and oxygen lack (From *Camps and Purchase* 1956 by kind permission of authors and publisher)

state is extremely critical immeasurable in fact with present-day biochemical techniques If the amount of narcotic is great the basal system is also affected and tissue respiration becomes measurably depressed

CHAPTER 19

ANOXIC STATES AND THEIR TREATMENT

B G B LUCAS

AT THE beginning of the present century anoxia was defined by Haldane as no oxygen in the body but it was not until a few years later that Barcroft (1920) clarified this to mean a failure of oxygen to reach the tissues and classified anoxia into three groups, as follows

Anoxic in which oxygen cannot gain access to the blood stream

Anaemic in which the blood is incapable of carrying a sufficient quantity of oxygen for the tissues

Stagnant where for some reason the circulation fails

After the World War I Peters and Van Slyke (1931) added a fourth group *histotoxic* in which the cell is poisoned so that oxygen, although freely available in the blood stream cannot be utilized by the tissues

If the definition of oxygen lack is modified to mean not only absence of oxygen but also inability to use it cellular or histotoxic anoxia can be further subdivided into four (Fig 27) according to the way in which the metabolism is affected

Extracellular histotoxic anoxia is that in which the tissue oxygen enzyme systems of the body are poisoned The classical example is cyanide poisoning where the cytochrome enzyme system is destroyed resulting in the immediate death of the cell The action of most hypnotic drugs can also be included as they depress enzyme activity and have been shown to inhibit cellular respiration in the brain It has been suggested (Butler, 1950) that narcotics must have some other action because the concentration of drugs necessary to depress cellular respiration *in vitro* is many times greater than that which is necessary to achieve unconsciousness *in vivo* but one theory has been postulated which overcomes these objections while retaining the basic principles (McElroy 1947) This is that the central nervous system has two parallel systems for metabolism The first or basal system keeps the cell alive and is dependent upon the breakdown of carbohydrate which in turn depends upon the presence of tissue enzyme activity The second or energy system is responsible for the production and breakdown of adeno sinetriphosphate (ATP) a high energy phosphate which enables the cell to function and emit energy ATP is known to be the basic source of utilizable energy inside the cell and it is concluded that hypnotic agents act at the site of ATP synthesis or breakdown, so inhibiting energy production resulting in unconsciousness The amount of ATP in the cell is minute and so the rate of production and break down must be rapid if the cell is to produce energy continuously With such a rapid turnover it follows that the change from the conscious to the unconscious

oxygen and 5 per cent carbon dioxide was started immediately A lumbar puncture was performed the pressure being 200 millimetres of water and cerebrospinal fluid was allowed to flow out slowly until the pressure fell to 140 millimetres At the same time a transfusion of one pint of concentrated red cells was given After one hour respiration started spontaneously after six hours he showed signs of returning consciousness The next day he was completely decerebrate He sat propped up in bed with his eyes closed and a mask like expression on his face and showed no signs of intelligence whatsoever He would drink and swallow if anything were placed in his mouth and exhibited a perfect physiological rage reaction when pinched he snarled his face contorted with rage and he moved his limbs freely but this movement bore no relation to the site of the painful stimulus Normally the limbs remained in a state of flexion the muscles being hypertonic and the plantar response a mass withdrawal The other systems of the body showed no abnormality He existed like this without any recovery for a further seven days finally dying in a state of hyperthermia

STAGNANT ANOXIA

Stagnant anoxia is seen in cardiac failure Clinically, however cardiac failure is not usually considered to be an anoxic state and further confusion is caused by using the clinical terms peripheral and central cyanosis Presumably peripheral cyanosis indicates a stagnant circulation, and yet there are occasions when the cerebral circulation is so slowed that there is insufficient oxygen available from the blood stream the so called central cyanosis an example being the fainting attacks of the very hypotensive subject The mental confusion seen in patients with arteriosclerosis may be due to a diminished blood supply reaching the brain

HISTOTOXIC ANOXIA

In all the classical cases it is common to find other types of anoxia as well, for example in barbiturate poisoning or deep anaesthesia there is usually under ventilation which produces a retention of carbon dioxide, the metabolite anoxic effect of which is often ignored

Case III Male 14 years was admitted to hospital suffering from concussion and multiple fractures after falling 40 feet Following anaesthesia and the setting of his fractures he was nursed in the Trendelenburg position and given continuous oxygen by means of an ordinary anaesthetic mask and machine with partial rebreathing and a relatively small flow Prior to being connected to continuous oxygen his blood pressure was 120/80 millimetres of mercury and he was quite well and semiconscious During the next three hours his condition deteriorated with deepening coma and fall of blood pressure to 60/50 millimetres of mercury pulse 140 and respirations 44 His colour was good although there was extreme vasodilatation When the oxygen was removed and he was placed level he recovered consciousness within thirty minutes and his blood pressure rose to 110/70 millimetres of mercury In this case the re breathing without carbon dioxide absorption plus the defective ventilation brought about by the Trendelenburg position was responsible for a marked respiratory acidosis which together with the remains of the anaesthetic agent and the concussion caused deep unconsciousness

In *pericellular histotoxic anoxia* oxygen cannot gain access to the cell due to a decrease in cell membrane permeability such is occurs with lipoid soluble anaesthetic agents for example chloroform or ether

Substrate histotoxic anoxia indicates insufficient foodstuff for efficient metabolism In brain cell respiration hypoglycaemia, that is a lack of carbohydrate in the circulating blood, has exactly the same effect on the cell as a lack of oxygen

In *metabolite histotoxic anoxia* the end products of cellular respiration cannot be removed so preventing further metabolism as is found in uraemia or carbon dioxide poisoning

Anoxic states can arise from a variety of causes but the most important features are that the effect on the cell is the same whatever the cause and that combinations of types summate their individual effects as illustrated in Fig 27

ANOXIC ANOXIA

Anoxic anoxia alone is seen in industry following accidental exposure to asphyxiant gases or at high altitudes due to low oxygen partial pressure or in combination with metabolite anoxia in asphyxia following strangulation drowning or some other obstruction to the air passages such as the inhalation of vomit, laryngeal oedema haemorrhage into the thyroid gland and so on

Case I Female 18 years previously fit was operated upon for an adenoma of the thyroid under endotracheal cyclopropane anaesthesia Operation and return to full consciousness were without incident Six hours after operation a slight stridor developed and the patient complained of difficulty in breathing Four hours later she was cyanosed and very dyspnoeic Oxygen was given somewhat ineffectually through double nasal catheters and her condition soon worsened until 14 hours later (that is 24 hours after operation) she was practically unconscious very restless distressed and incoherent An endotracheal tube was passed and continuous oxygen given Immediately her colour returned to normal her general condition improved and her pulse dropped from 130 to 90 Mentally there was no improvement she was confused and emotionally unstable The following day her condition was unchanged and the tube was removed but immediately replaced and the oxygen continued as the signs of obstruction at once made themselves manifest That evening her mental state was much worse and by morning she was comatose Her pulse and temperature both started to rise and by evening (3½ days after operation) she was deeply unconscious with a pulse rate of 160 and a temperature of 103 F She died early the following morning The anoxic damage in this case had occurred during the 14 hours of partial asphyxia due to the presence of laryngeal oedema

ANAEMIC ANOXIA

Pure anaemic anoxia due to anaemia is relatively uncommon because patients with such a condition usually die before treatment can be effected but it is seen in carbon monoxide poisoning or methaemoglobinaemia In these conditions the functioning haemoglobin is bound up into permanent compounds which cannot take up oxygen and so the oxygen content of the blood is reduced

Case II Male 47 years was admitted to hospital following exposure to coal gas When first seen he was bright red in colour pulse rate 90 blood pressure 70/50 millimetres of mercury and respirations almost imperceptible Artificial respiration with

there is a failure of the temperature regulating mechanism and hyperpyrexia of 108° F to 110 F may be present

Mild anoxia

With mild anoxia there is mental confusion and the patient is irrational and frequently lapses into deep sleep Reflexes are normal and recovery is fairly rapid but the patient may have complete amnesia of the anoxic insult and of several hours preceding it Some mild cases may drift into unconsciousness in a matter of hours because of the increasing effect of the intracellular oedema and be barely rousable They will respond to painful stimuli in a conscious way, although most reflexes will be diminished Recovery occurs even after many days of unconsciousness, but the return to normal may take many months during which time there may be variable neurological and psychotic signs

Case IV Female 53 years about to have a stitch abscess incised following a subtotal thyroidectomy three weeks previously was induced with 400 milligrams of thiopentone Almost immediately her heart stopped The abdomen was opened within four minutes and the heart palpated and found to be dilated and inactive Massage was started and at the same time an intracardiac injection of adrenaline was given Immediately following the injection the heart started beating and within a few seconds produced an adequate carotid pulse Respiration did not return for a further twenty minutes By the time the abdomen was closed the patient was breathing quietly and had a normal pulse and blood pressure but she was unconscious and had no reflexes She did not recover consciousness for two days during which time she passed through stages of being acutely spastic and apparently decerebrate When consciousness returned she was neurologically normal but completely deluded and irrational During the next two months she improved slowly She first passed through a phase of being completely child like only remembering her maiden name and incidents in her early life and later of being a young married woman She continued to improve and three months after the original cardiac arrest she was discharged from hospital normal apart from having a somewhat facile personality One year later there was no psychiatric neurological or other evidence that she was in any way different from prior to her cardiac arrest

Duration of decerebrate state

If the anoxia results in a decerebrate state lasting more than 72 hours complete recovery will not occur and death usually ensues within one to six weeks There are occasional exceptions as the following example shows

Case V Male 8 years suffered cardiac arrest during bronchography under general anaesthesia and cardiac massage was not started for at least six or seven minutes Ultimately the heart and respiration restarted but 24 hours later the child was deeply unconscious and completely flaccid During the next few days he showed all the signs of decerebration with a slowly increasing spasticity Gradually his spasticity lessened and after one year he was a typical decerebrate vegetable He would cry in response to painful stimuli and would eat if food were placed in his mouth but he was incapable of making any coordinated movements Six years later he had grown and was of normal height and weight for his age but was unchanged neurologically The only sense he appeared to have was that of hearing in as much as he would start at a loud noise He had the typical appearance of one whose brain has been destroyed (Fig 28)

SIGNS AND SYMPTOMS

Unconsciousness

As the brain is the organ most sensitive to oxygen lack it follows that the main characteristic of an anoxic state is unconsciousness This will vary in depth according to the severity of the insult but so far as the central nervous system is concerned it is impossible to decide what anoxic agent has been the cause The physical signs of different levels of unconsciousness from anoxia are the same as those of similar levels from anaesthesia but differ from those following head injury in as much as in anoxia the signs alter because of the after effects of the anoxic insult on the brain cell Anaesthetic agents are said to be unlike ordinary histotoxic poisons since the cell recovers completely when the drug is removed This is true if the depth and duration of anaesthesia are not too great but post anoxic states are seen under certain conditions following deep anaesthesia especially in old subjects Anaesthesia can be considered to be a mild state of anoxia which is reversible, whereas anoxia from other causes may cause irreversible changes in the cell

Cellular effects

Fundamentally when the metabolism of a cell is reduced there is first a short period of stimulation then paralysis and finally death of the cell there being a great difference between the paralytic stage and death If the reduction of metabolism is severe during the paralytic stage certain intracellular electrolytic changes occur which exert an effect after the anoxia has ceased there is a loss of intracellular potassium with a consequent rise in sodium This increase in intracellular sodium causes retention of water in the cell that is an intracellular oedema This oedema prevents the cell from functioning normally for some time after the anoxic insult has been withdrawn and may be so severe that the cell becomes distended and ultimately disrupted When this happens the anoxia produces irreversible changes There is some evidence that the intracellular oedema does not occur until the anoxic insult has been removed and reaches a maximum effect after six to eight hours During this time the signs of unconsciousness will vary For example, during certain intracardiac operations under hypothermia the cerebral circulation may be arrested for several minutes At the end of the operation the patient may be conscious and rational but during the next eight hours he may become sleepy and confused, not returning to normal for a further twenty four hours

Early stages

In the early stages following severe anoxia all the reflexes will be absent apart from the light reflex Later there may be a stage of irritability when the reflexes will be exaggerated Respiration may vary from the quiet breathing of light unconsciousness to the terminal jaw tugging type which is seen with medullary failure The heart rate is usually increased but there is a state of vasoconstriction with a slight fall in blood pressure—an indication of a diminished cardiac output In profound damage from anoxia when there is complete destruction of the vasomotor centres the systolic blood pressure falls to about 60–70 millimetres of mercury Anoxia *per se* has little effect on temperature, except terminally when

performed Two years later his colour was good his haemoglobin had dropped from 140 per cent to 100 per cent, and he had gained many pounds in weight In order to assess the result of the operation it was decided to recatheterize him and because he had tolerated the previous dose of thiopentone it was repeated This time he became so deeply unconscious that he had to be resuscitated for several hours and the catheteriza tion had to be abandoned

To prognosticate about the ultimate outcome of the post anoxic unconscious subject is not easy With some patients being ventilated and fed artificially there may come a time when continuation of this artificial means of maintaining life appears pointless A practical guide is that if the signs of unconsciousness change during the first 72 hours some recovery may be possible, but if there is no altera tion, therapy can be abandoned after seven days A terminal sign is a progressive hyperpyrexia and death will occur at temperatures as high as 110° F

TREATMENT

Effective ventilation

The main feature in the general treatment is the handling of the unconscious patient so that he does not succumb to some secondary complication Effective ventilation to ensure that the blood is fully oxygenated and carbon dioxide eliminated is essential Often the respiratory centre will be depressed by the anoxic insult so that some form of assisted respiration is necessary The method is unimportant, provided an adequate minute volume is maintained and can be performed either by manual 'bag squeezing with a carbon dioxide absorber or by means of any intermittent positive pressure breathing machine Even in those cases in which respiration is only slightly depressed the under ventilation if uncorrected will cause further anoxia from carbon dioxide retention and the respiratory centre may fail completely within a few hours

To enable artificial respiration to be done effectively the patient must be intubated but if unconsciousness persists for more than 24 hours, a tracheotomy should be performed This not only prevents trauma to the larynx, but enables the patient to be nursed more easily and allows intermittent suction of the bronchi to remove the accumulation of secretions Survival following prolonged un consciousness is primarily a nursing triumph bronchial toilet is most important together with repeated change of position and physiotherapy The bladder must be kept empty with the aid of an indwelling urethral catheter and a complete cover of antibiotics used to prevent infection anywhere

Hypothermia

Following anoxia the thermoregulating centre may be affected, giving rise to hyperthermia For this reason the patient must be cooled deliberately until full consciousness is regained or for a period of 7 days The immediate application of hypothermia to 32°–33° C is of particular value in protecting the brain from the after effects of the anoxic insult by reducing the oxygen demand, but after 8 days no treatment will be of any avail

Resting the heart

Apart from the brain the heart is the only other organ likely to be affected by the anoxia and it should be rested as much as possible An electrocardiogram taken

PROGNOSIS

Pure anoxic anoxia as seen at high altitudes has a good prognosis and it is unusual for such patients if they recover, to have any residual neurological sequelae This is also true of those with barbiturate poisoning, provided adequate resuscitation is undertaken immediately On the other hand, anaemic anoxia, particularly carbon monoxide poisoning often leaves residual signs A combination of types, for example cardiac arrest, carries the worst prognosis Obviously the state of the

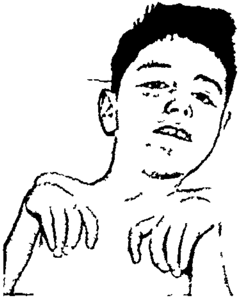


FIG 28 —Photograph of Case V six years after cardiac arrest

brain before the anoxia will alter the tolerance to the severity of the insult Hence anoxic resistance is reduced following shock haemorrhage, or anaesthesia

The young are more resistant than the old, but allowance must be made for the increased oxygen demand of children particularly at puberty and the fact that the available reservoir of oxygen in the lungs is reduced in babies The new born are extremely resistant to oxygen lack because for the preceding nine months they have been existing *in utero* at a very low oxygen tension This resistance persists in the normal for up to six weeks but children with congenital cyanotic heart disease maintain their resistance all their lives or until their condition is treated surgically Contrary to general opinion subjects with cyanotic heart disease are not anoxic at rest They have a low cardio respiratory reserve in as much as effort rapidly drops their oxygen supply and they become unconscious easily but at rest they are not incapacitated in any way Moreover, there is no evidence that these children are mentally backward, as one would expect if they were chronically anoxic Their resistance to oxygen lack is well shown by their tolerance to histotoxic anoxic agents such as the barbiturates

Case VI Male 7 years with Fallot s tetralogy who was extremely cyanosed under went cardiac catheterization under rectal thiopentone using a dose of 1 gramme per 30 pounds instead of the standard 1 gramme per 50 pounds This produced good sedation but not complete unconsciousness Subsequently a Blalock shunt operation was

TREATMENT OF CARDIAC ARREST

Principle

Cardiac arrest need not be lethal if oxygenated blood can be pumped to the brain within 3 minutes This means artificial respiration and cardiac massage as soon as the heart stops

Procedure

As soon as cardiac arrest has been confirmed

The Anaesthetist

1 Appoints a timekeeper who will call out minutes loudly
2 Commences artificial ventilation with oxygen intubating if possible

The Surgeon

1 Opens the left chest anteriorly through an intercostal incision (5th space) makes a small hole in the pleura before incising it so as to avoid damaging the lung
2 Inserts one hand and squeezes the heart rhythmically
3 Inserts and opens rib retractor so that both hands can be inserted into chest
4 Opens the pericardium inserts one hand behind the heart and massages with the other

The Nursing Staff

1 Send for rib retractor
2 Place 4 arterial tourniquets around all 4 limbs as high as possible
3 Prepare solutions of 10 millilitres of 1 per cent calcium chloride and 10 millilitres of 1/10 000 adrenaline for intracardiac injection
4 Send for electrical defibrillator

Effective massage will produce a carotid pulse

The emergency is now over and effective cardiac action can be restored at leisure

1 If the heart is toneless and blue massage more vigorously but allow time for the heart to fill between squeezes When it regains tone the heart will probably start but if it does not inject 5–10 millilitres of 1 per cent calcium chloride into the left ventricle If this does not produce a beat *inject 5 millilitres of 1/10 000 adrenaline into the left ventricle Do not repeat these* injections within ten minutes

2 If the heart is in ventricular fibrillation it will be blue and shimmering Massage vigorously *until tone and colour improve Fibrillation will now be coarser and slower Inject 5 millilitres of* 1/10 000 adrenaline into the left ventricle and massage for a further one minute Then defibrillate electrically by placing one electrode on either side of the heart insulating the electrodes from the *rest of the* chest as well as possible with pieces of rubber such as rubber gloves One or two shocks will be effective

When the heart starts watch for at least 30 minutes before closing the chest assisting with massage if the heart beat is feeble

If the heart stops during an abdominal operation an attempt can be made to massage the heart through the diaphragm by compressing it up to the chest wall But if the heart does not start beating within one minute this approach must be abandoned

continuously otherwise the acidosis itself becomes harmful Blood letting and transfusion with packed cells are also helpful in removing the carboxyhaemoglobin

Barbiturate poisoning

As soon as possible after resuscitation has been started the *stomach must be* washed out to remove any remaining barbiturate In the unconscious state the rate of absorption of these substances is very slow and considerable quantities may

at least 24 hours after the insult may reveal a current of injury pattern, or an inverted T wave, suggesting conductive tissue or myocardial damage Intravenous fluids, therefore should be reduced to a minimum and fluid balance and feeding should be maintained by intragastric or rectal means The electrolyte balance must be watched carefully, paying particular attention to sodium retention

Dehydration

Some form of dehydration therapy is desirable for the treatment of the intracellular oedema that occurs in the early post anoxic period The rectal administration of magnesium sulphate has been found to be of no value, but some success has been obtained with the intravenous administration of a 50 per cent solution of glucose or sucrose These solutions, however, are irritant to veins and may cause phlebitis and the best results have been achieved with four times concentrated plasma or serum given intravenously in a dose not exceeding 50 millilitres per hour There is some evidence that dilatation of the cerebral blood vessels, in addition to the dehydration therapy, is beneficial and histamine in a dosage of 1 milligram per 100 millilitres can be added to the intravenous solution for this purpose, a bilateral stellate block has also been recommended This dehydration therapy with or without attempted cerebral vasodilatation has been used most extensively following cardiac arrest The over all results have not been convincing partly because it is impossible in such circumstances to obtain satisfactory controls

Specific therapy

In certain anoxic states there is a need for specific therapy in addition to the general treatment

Cardiac arrest

The treatment of the post anoxic state resulting from this condition has already been described but it is relevant to mention the immediate problem of getting the heart and cerebral circulation restarted as soon as possible Time is of the greatest importance No definite period can be stated beyond which the brain will not recover but more than three minutes of cardiac arrest under anaesthesia in the adult human may result in permanent brain damage Oxygenated blood must reach the brain quickly hence the heart must function as a pump and oxygen be supplied to the lungs that is cardiac massage with efficient artificial respiration The only way to ensure success is for all members of the surgical team to be fully conversant with their respective duties beforehand and not to panic when the emergency arises The chart on page 293 delineates the duties of the theatre personnel and the regime which should be followed

Carbon monoxide poisoning

Following first aid treatment and after the patient has been admitted to hospital intermittent ventilation with 5 per cent carbon dioxide in oxygen should be started This mixture was first used for carbon monoxide poisoning by Henderson in 1916 and is probably one of the few occasions in medicine when the inhalation of such a mixture is of real value (Henderson 1916) The acidosis so produced aids the dissociation of carboxyhaemoglobin but carbon dioxide should not be given

CHAPTER 20

TRENDS IN THE MODE OF INVESTIGATION OF ANAESTHETIC PROBLEMS

RONALD WOOLMER

INTRODUCTION

IT is a commonplace that anaesthesia has improved, during the last twenty years, 'out of all recognition.' From the 'consumer's' point of view, it has become so good that there is little room for further improvement, and surprise is sometimes expressed, even by intelligent laymen, that there is still scope for research in anaesthesia.

It is true that if progress in anaesthesia could be represented graphically by plotting percentage of 'consumer satisfaction' against time, the curve would be an exponential one approaching 100 per cent, and if the area above this curve, tailing off with the advancing years, were taken to represent the field available for research into anaesthesia, this chapter would not be worth writing.

The 'consumer's' satisfaction, however, is not the asymtote by which to determine boundaries, and the field of research into anaesthesia is in fact widening rather than contracting. This is partly because the scope of anaesthesia increases *pari passu* with the scope of surgery and partly because of an increasing identity of interests between anaesthetists and workers in other fields.

It has been said of surgery—as it has of anaesthesia—that there are few worlds left to conquer, and it is true that no region of the body is now inaccessible to the surgeon. Each new advance brings bigger problems, and costs more in effort and in skill. What is now regarded, perhaps naively, as the last frontier of surgery—the unhurried reconstruction of the open heart—has still to be attained. The problems it poses are very much the concern of the anaesthetist, but they cannot be studied by him in isolation. Progress in this direction demands an integration of the efforts of workers in many fields, and it brings the anaesthetist into much closer contact than before with other specialists, to the benefit of all.

As advances become more difficult a higher standard of training and skill and greater technical resources are required. Nowadays, research into any of the biological sciences requires time, teamwork and technology. It also requires, if it is to be fruitful, a certain type of mind, one which does not form an opinion without a logical basis, which does not recognize a causal association until the evidence is decisive, which puts no value on an experiment that is not rigidly controlled, which is alive to the possibility of hidden variables. This type of mind is not very common, for human beings find it hard in all spheres to base their opinions on evidence rather than upon their hopes or prejudices (Russell, 1931).

be still present, even after 24 hours Opinion is divided concerning other specific therapy Analeptics such as picrotoxin, metrazol, bemigride and many others have been used by some (Koppanyi and Fazekas, 1952) The proponents of this therapy suggest that analeptics aid the breakdown of barbiturates so that recovery is hastened, but it is probable that they merely stimulate the brain temporarily, and do not hasten ultimate recovery However, the unconscious state will be lightened from time to time by the use of these drugs, which may be of assistance in the prevention of pulmonary complications Other workers (Nilsson, 1951) on the other hand, have demonstrated that if adequate physiotherapy is undertaken throughout the resuscitative period, and bronchial toilet done thoroughly, there is no reason to use analeptics Finally, it has been suggested that as the barbiturates poison the flavoprotein group of oxygen enzymes preventing the utilization of pyruvate, the administration of artificial substrates such as sodium succinate, or glutamic acid, might boost brain cell metabolism (Beyer and Latven, 1944) In theory the metabolism of these substances is unaffected by the barbiturates but the results of this therapy have been somewhat equivocal possibly because having to be given in a 5 per cent solution intravenously the resulting large volume of fluid is an embarrassment to the brain and the circulation

Asphyxia neonatorum

As the newborn are so resistant to anoxia asphyxia neonatorum is unlikely to produce neurological damage hence the urgency in the treatment of this condition is to establish respiration rather than treat the oxygen lack Analeptics or respiratory stimulants are of value only in so far as they might initiate breathing (*See also* Chapters 12 and 18)

REFERENCES

Barcroft J (1920) *Lancet* 2 485
Beyer K H and Latven A R (1944) *J Pharmacol* 81 203
Butler T C (1950) *Pharmacol Rev* 2 121
Camps F E and Purchase W B (1956) *Practical Forensic Medicine* London Hutchinson
Henderson Y (1916) *J Amer med Ass* 67 580
Koppanyi T and Fazekas J F (1952) *Amer J med Sci* 224 577
McElroy W D (1947) *Quart Rev Biol* 22 25
Nilsson E (1951) *Acta med scand* 139, Supp 253
Peters J P and Van Slyke D D (1931) *Quantitative Clinical Chemistry* Vol 1 Interpretations London Bailliere Tindall and Cox

schools in Britain he has to repeat a series of experiments which were first done by successful researchers many years ago If he sets up his apparatus and conducts the necessary operations correctly, the experiment works If it does not, he has done something wrong The theory is not brought into question This sort of work although not entirely without value does nothing to teach the principles of research All it does is to introduce the student to some of its tools and methods

Having made this nodding acquaintance with experimental methods the student leaves the laboratories behind, in most cases never to return to them

It may well be thought that this is an unsatisfactory basis for the training of research workers or for bringing out latent talent and some would say that because selection is admittedly very difficult, all students should undergo a course of training in research This view is exemplified by one of the medical schools in the United States of America There a course in biophysics is given during the clinical period It occupies the equivalent of two hours a week during term for a whole year It starts with mathematics and ends with instrumentation having touched on such subjects as hydrodynamics thermodynamics, osmotic energy atomic structure physical chemistry radiation cell growth and bio electric potentials The biological applications are illustrated by clinical cases or animal demonstrations Such a course should provide a valuable grounding in experimental methods and should give some idea of the scope of biological research but one wonders how much of the considerable effort involved in arranging it is wasted on the average student It could be said that if such a course resulted in even one really good man a year devoting himself to research it would be worthwhile but the competing claims of other subjects in the undergraduate curriculum make its adoption in Great Britain most unlikely

Undergraduate training

What then should be done at the undergraduate level to further a knowledge of and an interest in research and to bring out latent possibilities in this direction? The practical classes in physiology and applied pharmacology could be improved and a trend in this direction is already apparent in some of the medical schools in Great Britain and abroad Instead of repeating stereotyped experiments the class is divided into groups each of which is presented with one aspect of a problem The group has to discuss the problem realize its implications and devise a method of attack The method is then discussed with the instructor and each member of the group plays his part in setting up the apparatus and recording the results In many of the experiments the students themselves can be the subjects If they have an inspiring teacher students will willingly submit to considerable discomfort and it is interesting that an experiment performed upon oneself which involves discomfort or pain makes a much more lasting impression than if it is performed upon a colleague When the results have been collected and arranged each group gives an account of what has been done and their part in a composite study is fitted into its place In this way students can be given initiative and can be encouraged to worry out problems for themselves as well as gaining some familiarity with the tools of research

The other way in which undergraduates are brought into contact with research is by association with the people engaged in it, and one of the benefits which the prosecution of research confers on a medical school is from contact with people

It may be called for want of a better name the scientific mind and it uses as its natural instrument the scientific method Whether this type of mind can be acquired, or whether it is an inborn characteristic like red hair or left handedness is a matter of opinion There is no doubt that those lacking it are unlikely to do research of any value, whatever skill they may acquire in the methods

SELECTION OF RESEARCH WORKERS

It is often said that Great Britain is short of good research workers in most fields of scientific endeavour and universities and other teaching bodies are being urged to produce more but how is a potentially good research worker to be selected? Aptitude tests are applied—though without conspicuous success—in the appraisal of fitness for various industrial occupations but there is no aptitude test for fitness to do research It is sometimes thought that the potentially good research worker by his outstanding mental qualities and his keenness for investigation will thrust himself upon the attention of the authorities This may sometimes happen but the man who draws attention to himself is often not really fitted for a researcher s post Genius it has been said is 1 per cent inspiration and 99 per cent perspiration and the idea applies with equal force to research But the patient plodder with an inquiring methodical mind and perhaps an occasional flash of intuitive genius is not the one to attract attention though he may well have the stuff of which first class research workers are made

This problem of the selection of suitable people for research is a baffling one The more one tries to draw up criteria for selection the less certain one becomes that these are the right criteria and the more doubtful one becomes of one s ability to recognize them in any case An analysis of the characters of outstandingly successful research workers to find some common denominator—some group of characteristics common to them all—quickly results in despair

TRAINING RESEARCH WORKERS

If then it is admitted that there is no reliable means of selecting suitable personnel what steps must be taken to maintain the flow of research workers into the various branches of medical science?

Training in research if it is to be effective is expensive and time-consuming and it should not be wasted on unsuitable material On the other hand, unless students are given some contact with research latent possibilities cannot come to light

In Great Britain there seems to be no consolidated opinion among medical educators on the place of research in the medical curriculum. The practice differs from one school to another but in undergraduate teaching research plays little part

The first contact the medical student has with research—though very much at second hand—is during his study of the basic sciences When he is learning their theory he reads of the work of the pioneers who established it He is told how they planned their experiments and if he has sufficient insight he will be able to follow the workings of their minds In his practical classes in most medical

schools in Britain, he has to repeat a series of experiments which were first done by successful researchers many years ago If he sets up his apparatus and conducts the necessary operations correctly the experiment works If it does not, he has done something wrong The theory is not brought into question This sort of work although not entirely without value, does nothing to teach the principles of research All it does is to introduce the student to some of its tools and methods

Having made this nodding acquaintance with experimental methods the student leaves the laboratories behind in most cases never to return to them

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who are carrying out original work and pursuing original ideas This contact need not occur in the laboratory itself but over the luncheon table or in the hospital mess, and it provides a good reason for research workers not being ivory towered' The unforced introduction to research which may result from an informal contact of this sort can sometimes be the means of recruiting to the ranks of research good men who would not otherwise have joined them

It is evident that the opportunities for teaching research to undergraduates in Great Britain are limited, but that better use is being made of them than in the past

Postgraduate training

After qualification there is a case for providing instruction in research for the selected few The difficulty here is one that has already been discussed—that of selection A voluntary basis has been advocated, on the theory that those who are keen on research and therefore presumably have an aptitude for it will be the ones to come forward This is an obvious *non sequitur*, for it does not follow that one who is ' keen on research will be any good at it nor that those who do not volunteer would not be the right types The only argument in favour of selection on a voluntary basis is that no one has been able to devise a better method

Having then collected a group of postgraduate students for instruction in research , how is one to proceed? Should one concentrate on principles or methods? The principles of research are not amenable to didactic teaching To the possessor of the scientific mind they are self evident To him who lacks it they will always be elusive If one decides to concentrate on methods, in the hope that principles will arise from them one is faced with the question What methods? That excellent American publication *Methods in Medical Research* has already grown to six volumes What techniques what instruments, what groups of methods should be taught? In investigating the problems of anaesthesia one may encounter a range of apparatus from a Douglas bag to a scintillation counter and a range of techniques from cardiac catheterization to electro encephalography The means of investigation can be devised only after the plan of attack has been formulated and a technique may have to be evolved to suit each individual problem Whatever methods may be learned, therefore they will probably be the wrong ones for the problem the student may wish to investigate later This is of no importance however and the methods he does learn should be taught, not for their practical usefulness, but merely as illustrations of a principle

One has to decide too whether a group of students can be introduced, as a class to the principles and practice of research, or whether it is better for them to be spread out, as thinly as possible among the departments in which research is going on It would seem that the latter method is preferable although the difficulty of finding effective places for a group of students in this way is formidable

Another method of bringing postgraduate students into the research field is by requiring a graduate who embarks on a course of study in some special subject to spend some time—usually a year— doing research This has been called research at the gunpoint Its adoption does something to increase the volume of research work, it does nothing to improve its quality although doubtless some thing of value sometimes results from it

Although this book is intended for anaesthetists anaesthesia itself has so far

hardly been mentioned in this chapter This is because biological research is indivisible It differs from research into inanimate things because account has to be taken of biological variation This has a great influence on the design of experiments and it means that appropriate statistical techniques must be applied to the interpretation of results But biological research requires the same sort of approach in most of its branches and a research worker properly trained in one subject should be able to adapt himself without much difficulty to another

PROBLEMS FOR ANAESTHESIA RESEARCH

There are a number of problems which should engage the attention of the research anaesthetist, but for the solution of most of them close co-operation with workers in other fields is a necessity

Evaluation of new drugs

Some of these problems concern the evaluation of new drugs Here the investigating anaesthetist must align himself mentally with the pharmacologist Anaesthetists have too long been held in thrall by the clinical impression , which is not only worthless but may be positively harmful The anaesthetic room and the operating theatre provide excellent opportunities for extending into the clinical field work which has been started on animals in the pharmacological laboratory It is true that conditions are not susceptible to anything like such close control by the experimenter and a large proportion of experiments may be rendered valueless through this This disadvantage can to some extent be mitigated by careful planning of experiments and the use of proper statistical methods and it may be offset too by the sheer volume of clinical material available if it is used intelligently There is a welcome trend in the direction of extending the scientific methods of the pharmacological laboratory into the clinical domain of the hospital but much progress has to be made in this direction and drugs which have not been subjected to anything resembling a scientifically conducted clinical evaluation are still too often released prematurely to the medical and even to the lay public This situation is not likely to improve until we have more research workers able and willing to carry out clinical trials men who are capable of designing an experiment which will distinguish between the merits of two different drugs or techniques who are aware of such pitfalls as the placebo response who have a sufficient volume of clinical material at their disposal and who are able to present their results in a simple and unequivocal way

Other problems concern issues more fundamental to anaesthesia such as the precise mode of action of anaesthetic and analgesic drugs about which one is still much in the dark This problem is being attacked on several *different fronts* but though it concerns anaesthesia so closely progress can be looked for from the enzyme chemist and not from the anaesthetist

Mechanism of consciousness

A fascinating field of research concerns the mechanism of consciousness a field which borders on anaesthesia psychiatry and neurophysiology As the

who are carrying out original work and pursuing original ideas This contact need not occur in the laboratory itself but over the luncheon table or in the hospital mess, and it provides a good reason for research workers not being ivory towered The unforced introduction to research which may result from an informal contact of this sort can sometimes be the means of recruiting to the ranks of research good men who would not otherwise have joined them

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CONCLUSIONS

To sum up the trend in research into anaesthetics appears to be in the direction of broadening the confines of the subject of a more rigorous application of the scientific method of an increasing appreciation of the importance of physics and of a greater tendency towards co operative effort

REFERENCES

Methods in Medical Research (1948–54) Vols 1–6 Chicago Year Book Publishers
Russell 3rd Earl B A W R (1931) *The Scientific Outlook* London Allen and Unwin
Trotter W (1941) *Collected Papers* Oxford Oxford Medical Publications.

depressant power of the anaesthetist s drugs is directed more at the motor and less at the sensory side, the 'state of mind of a surgical patient becomes increasingly important To the inquiring anaesthetist this opens new fields concerned with the mechanism of wakefulness, the perception and appreciation of pain, the psychological effects of unremembered stimuli, and the mode of action of the tranquillizing drugs A great deal of work in these fields is going on None of it can be done by the anaesthetist alone but he can play an important part in it by his cooperation with others

Respiration

Other problems concern respiration, and they require the cooperation of the respiratory physiologist and the chest physician Lung function tests, lung compliance, the influence of assisted respiration on pulmonary mixing and perfusion, the design of breathing circuits and the problem of carbon dioxide clearance are all receiving attention The experience and the resources of the Services in aviation medicine and submarine activities are important in this connexion

Techniques for cardiovascular surgery

Progress in anaesthesia must always be concerned with the advancing frontiers of surgery and research anaesthetists are therefore interested in the development of techniques for cardiovascular surgery in general, and for surgery of the open heart in particular Much work is being done—by teams in which anaesthetists have their place—on artificial circulations on the possibility of arresting and restarting the heart by drugs, on the effects of hypothermia and on the early detection of cerebral hypoxia

Safety of anaesthesia

Another very important and practical field of investigation is the safety of anaesthesia and the causes of mortality and morbidity The furtherance of these inquiries requires planning organization and a correct statistical approach but it is one of the few subjects which can be investigated by anaesthetists independently

The importance of physics

It will be seen then that anaesthesia in its broadest sense offers a wide range to the research worker who is prepared to be one of a team The tools and the techniques which can be useful to him—and of whose potentialities he must be aware—are increasing rapidly A research team cannot be fully effective unless it can use the applications of electronics the various types of mechano electric transducers the physical methods of gas analysis tracer techniques and the numerous measuring and recording devices which physical science is making available

There is an important trend therefore to give increasing emphasis to physics in anaesthetic research departments, and it is now common for a physicist to be a member of the staff

the specialty would hardly attract talented recruits In 1950 the establishment of the Scandinavian Society of Anaesthesiologists permitted the interests of anaesthetists in these countries to be represented by a single association

The first generation of anaesthesiologists in Scandinavia have had no time for research all their time has been devoted to practical clinical work and to convincing their colleagues and Hospital Boards of the value of anaesthesia in the hands of experts It has been necessary to train a large number of young doctors for the new anaesthetic units in various hospitals—a task not always easy especially as the number of vacancies exceeded the number of competent applicants Owing to this demand some positions were occupied by doctors without satisfactory training or experience This is no longer necessary but was perhaps initially unavoidable It may be regarded as one of the teething troubles liable to occur in any young specialty In the Scandinavia of today the training and knowledge necessary for qualification as an anaesthetist are well defined Moreover remuneration is now such as to attract bright and promising recruits With this recruitment of young talented doctors progress in the more scientific aspects of anaesthesia might also be expected time will tell

Against the background of this brief review of the history of anaesthesia in Scandinavia, it might be of interest to indicate some of the problems which have attracted the interest of Scandinavian anaesthetists and some of the contributions they have been able to make

MUSCLE RELAXING EFFECTS OF ETHER AND CURARE

The clinical introduction of curare in 1942 as an anaesthetic adjunct soon gave rise to new problems thus Gross and Cullen (1943) reported a synergistic effect between ether and curare Each substance when administered by itself produced muscle relaxation supposedly by the same mode of action yet were synergistic when used together Naess of Oslo and Secher of Copenhagen investigated this phenomenon Naess (1950a b and c) was able to show that ether has a depressing effect on the function of the motor endplates in striated muscle He also reported on the basis of myographic studies that the effect of ether on the motor endplates was essentially similar to that of curare and that the two drugs were synergistic However the appearance of the myogram following the administration of ether differed somewhat from that seen after the administration of curare therefore it did not seem justifiable to assume that the two drugs had identical effects on the motor endplates

Secher (1950 1951a b c d) used the rat s diaphragm nerve-muscle preparation to investigate this problem and showed that ether is a strong muscle relaxant and that it will depress muscle contractions elicited by indirect stimulation The effect of ether was thus not on the muscle fibre as such On further investigation Secher was able to show that the combined muscle relaxing effects of curare and ether were cumulative and not synergistic Secher also produced evidence which indicated in his opinion that ether acts upon the motor endplates By studying whether the effect of ether on the endplates could be reversed by a curare antagonist neostigmine Secher endeavoured to find indirect evidence of these two drugs having an identical effect Neostigmine had an antagonistic effect but with a lower concentration By administering twice the dose of neostigmine the drug produced

CHAPTER 21

DEVELOPMENT AND TRENDS IN ANAESTHETIC RESEARCH IN SCANDINAVIA

ERIC NILSSON

WHEN a new medical specialty begins to develop in a country various factors prevalent at that time direct the evolution in a certain direction Anaesthesiology is a new specialty in Scandinavia a specialty which during World War II proved a necessity not only because of the rapid advances being made in surgery but because of progress in other branches of medicine

Dr Ralph M Waters once said that the development of a new specialty depends on three things a number of men each willing to put his shoulder to the wheel and get the wagon moving a journal and an organization to arrange meetings for discussion and exchange of thoughts and knowledge To these three requirements a fourth might be added namely opportunities for research in the new branch for without research no specialty can flourish

DEVELOPMENT

Anaesthesia as a specialty in Scandinavia is about 15 years old When the new Karolinska Sjukhuset in Stockholm was opened in 1940 its staff included an anaesthetist This specialist Dr Torsten Gordh had received his training in the United States of America under the direction of Ralph Waters However Gordh remained the only Swedish specialist anaesthetist for some years afterwards Thus progress was slow during the first few years and very few men chose anaesthesia as their specialty At that time it was necessary for such aspirants to the specialty to seek training abroad and during World War II Sweden was cut off from the rest of the world However after the war anaesthesia made tremendous strides forward Many young doctors went to the United States and England and after a few years training returned not only to continue research in the particular field in which they had become interested but to teach an ever increasing number of students and young doctors interested in this specialty Recruiting was thus facilitated for it was now no longer necessary to travel abroad to learn New hospital departments of anaesthesia were established and numerous vacancies for anaesthetists were witness to the demand The specialty now began to get what it needed

It became apparent that there was a need for some organization of anaesthetists and in Scandinavia national associations were founded in 1949–50 since when several new organizations have been formed to protect professional interests It was soon realized that unless the remuneration of anaesthetists was acceptable

the frequency of neurological complications can be reduced to practically zero Liljedahl (1955) investigated the prolongation of the effect of spinal anaesthesia by the incorporation of a vasopressor in the anaesthetic He found noradrenaline to be a suitable drug for this purpose He also discussed the causal relationship between a prolonged effect and the resorption mechanism of the anaesthetic combined with noradrenaline

SUXAMETHONIUM

In 1952 Thesleff published a thorough experimental and clinical investigation of suxamethonium He provided clinicians with an effective rapid and short acting muscle relaxant which in some respects must be regarded as superior to others available

Since its introduction suxamethonium has also found wide clinical use for many purposes other than in anaesthesia Suxamethonium would seem the best available agent to protect against skeletal fractures during electroconvulsive therapy Thesleff has continued his pharmacological studies on suxamethonium and his latest observations suggest that it might be necessary to revise our conception of the mode of action of muscle relaxants upon the endplates and of so called depolarization following administration of suxamethonium (Thesleff 1955)

NARCOTIC POISONING

Today the anaesthetist is not solely devoted to the relief of pain during operative surgery but plays a part in several other branches of medicine Above all he can contribute to the management of patients who have lost consciousness In Scandinavia as in many other countries poisoning with sedatives and narcotics has become an ever increasing social problem during the last few decades It is therefore natural that when anaesthesia was recognized as a specialty its representatives were employed in the resuscitation and treatment of these desperately ill patients

Since 1949 there has been in Copenhagen a detoxication centre under the direction of Carl Clemmesen He has long been interested in the therapy of cases of poisoning and excellent results have been achieved in his department Some of the members of that institute have investigated the different stages in the development of intoxication and their results are among the best of their kind in the world

Kirkegaard (1951) of Copenhagen drew attention to the undesired effect of barbiturates on the circulation in these patients He pointed out that they presented a classical picture of shock and that therapy must be directed towards the treatment of this condition if the patient is to be saved from his coma By the introduction of adequate shock resuscitation the mortality could be reduced

Nilsson (1951) questioning the value of central analeptics assailed the prevalent opinion which regarded central nervous stimulants as a necessary part of the treatment In a large clinical series he showed that with adequate treatment of the circulation collapse together with conservative prophylaxis against pulmonary complications and anoxia during the different stages of intoxication the mortality could be reduced very considerably Since 1950–51 this type of therapy has been

a further blocking effect on the motor endplate, which enhanced the effect of the ether. This did not occur when curare was used and was accepted by Secher as evidence that curare and ether differ in their qualitative effects on the motor endplates. The investigations of Naess and Secher have shed some light on anaesthetic problems of general interest and have considerable practical implications in anaesthetic practice, especially regarding the combination of ether and curare and the antagonist neostigmine.

ANAESTHETICS AND THE CIRCULATION

Another field of research on which anaesthetists in Scandinavia, especially in Stockholm and Uppsala, have focused interest is the effect of anaesthetics on the circulation. A number of both experimental and clinical investigations into this problem have been carried out. The first was by Gordh who in 1945 published his investigation on the effect of postural changes on the circulation in animals and men during anaesthesia. He showed the profound effect of lowering of the head on the venous return to the heart, on the blood pressure and respiration, which is so important in the practical management of shock. In recent years Johnson (1951) and Norlander, Troell and Åberg (1954) of the same hospital have concentrated on other circulatory changes during and after anaesthesia. Johnson studied particularly the distribution of blood during and after operation. With a catheterization technique he was able to elucidate the function of the lung as a blood reservoir and the changes occurring in it under different types of anaesthesia. Norlander, Troell and Åberg (1954) studied the changes in total haemoglobin and effective blood volume during and after anaesthesia and surgical intervention as well as the role played by noradrenaline.

Wiklander (1956) presented an excellent evaluation of different methods available for the determination of the effective blood volume during anaesthesia and operation. He compared the Evans blue dye method, the radioactive phosphorus method and the alveolar gas method and arrived at important results of clinical value. Holmdahl (1956) in a very interesting monograph discussed alveolar diffusion oxygenation during apnoea and its significance in animal experiments and in clinical work. In an era of clinical anaesthesia in which total apnoea produced by various muscle relaxants is a daily occurrence, this monograph has much to teach those interested in animal experiments and in anaesthesia.

SPINAL ANAESTHESIA

Spinal anaesthesia has been very popular in Scandinavia. This is due to the advantages it had to offer over other types of anaesthesia which were available in the past. The complications of spinal anaesthesia have also been made the subject of detailed investigations, as is witnessed by a number of publications, especially the monographs of Thorsén (1947), Arner (1952) and Liljedahl (1955). Thorsén and Arner directed attention mainly to the neurological complications attending this form of anaesthesia and arrived at somewhat different conclusions. Thorsén found such a high rate of serious neurological complications that he questioned the value of spinal anaesthesia except for a very narrow range of indications. Arner, on the other hand, showed on clinical material that with a refined technique

the frequency of neurological complications can be reduced to practically zero. Liljedahl (1955) investigated the prolongation of the effect of spinal anaesthesia by the incorporation of a vasopressor in the anaesthetic. He found noradrenaline to be a suitable drug for this purpose. He also discussed the causal relationship between a prolonged effect and the resorption mechanism of the anaesthetic combined with noradrenaline.

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practised at the Detoxication Centre in Copenhagen and used on about 1,000 patients per year Resuscitation from poisoning with sedatives has failed in only 1–2 per cent of cases

When coma in intoxicated patients treated conservatively is prolonged other complications are liable to occur Sometimes renal damage with anuria is seen and then there should be no hesitation in using dialysis with an artificial kidney to carry the patient over the critical period Early intravenous therapy with the addition of noradrenaline appears to be effective in the avoidance of hypotension with resulting renal injury in intoxicated patients The new barbiturate antidote bemegride (Megimide) is undergoing a trial by Clemmesen but it will have to be very effective to lower the present mortality

POLIOMYELITIS

In 1952 when the severe epidemic of poliomyelitis occurred in Denmark there was an immediate demand for mechanical respirators The severity of the epidemic is reflected by the large number of patients who had respiratory paralysis in the acute stage The epidemiologists then sought help from the anaesthetists Under the direction of Ibsen and Weino Andersen a temporary organization was rapidly established and the lives of many patients were saved by manual artificial pulmonary ventilation This was something new in the therapy of poliomyelitis and it was from the experience gained in operating theatres with this type of artificial respiration which enabled the anaesthetists to be of such assistance In this way respite was gained so that the entire organization could be modified along new lines in which epidemiologists laboratory workers otolaryngologists and anaesthetists worked together successfully Many urgent problems arose which required clinical research during the actual epidemic The results achieved have been described in several publications (Ibsen Weino Andersen and Lassen 1954 and others) and the contribution of anaesthetists on that occasion was the main subject of the third congress of Scandinavian Anaesthesiologists held in Copenhagen in 1954

FUTURE TRENDS

In recent years departments of anaesthesia have been created in Scandinavia especially at the university hospitals and now there are a sufficient number of anaesthetists to permit them at least some time for research A new Scandinavian Journal *Acta Anaesthesiologica Scandinavica* has appeared in the course of 1957 and it is the hope that it will promote research in Scandinavia Of the problems that are receiving attention in Scandinavia mention might be made of the field of hypothermia in Copenhagen and in Lund Malmo the mode of action of certain muscle relaxants (Lund) some changes in pulmonary function during operation and anaesthesia (Stockholm) certain new aspects of tetanus (Copenhagen) and investigation of certain effects of plasma substitutes (Oslo) The Kommune hospitalet in Copenhagen now has first class electronic investigational equipment It is thus apparent that although publications from Scandinavia have as yet been scanty research is going on and it is hoped that a greater contribution to the knowledge of anaesthesia will be made in the near future

BIBLIOGRAPHY AND REFERENCES

Arner O (1952) *Acta chir scand* Suppl No 167
Clemmesen C (1956) *Lancet* 2 966
von Dardel O and Thesleff S (1952) *Acta chir scand* 103 5
Gordh T (1945) *Acta chir scand* Suppl 102
Gross E G and Cullen C (1943) *J Pharmacol* 8 358
Holmberg G and Thesleff S (1952) *Amer J Psychiat* 108 872
Holmdahl M H (1956) *Acta chir scand* Suppl 212
Johnson S R (1951) *Acta chir scand* Suppl 158
Ibsen B Weino Andersen E and Lassen H (1954) *Proc 3rd Congress of Scand Soc Anesth*
Kirkegaard A (1951) *Undersogeeser over den Svaere Akutte Barbiturat forgiftuing* Copenhagen Munksgaards
Liljedahl S O (1955) *Acta chir scand* Suppl 202
Louw A and Sonne M (1956) *Ugeskr Læg* 26 761
Naess K (1950a) *Acta physiol scand* 20 Fasc 2-3
— (1950b) *Ibid* 20 Fasc 2-3
— (1950c) *Ibid* 19 Fasc 4
Nilsson E (1951) *Acta med scand Suppl* 139
Norlander O Troell L and Åberg B (1954) *Acta chir scand* Suppl 196
Pedersen J (1956) *Lancet* 2 965
Poulsen T and Secher O (1949a) *Acta pharm tox Kbh* 5 Fasc 3 196
Secher O (1950) *Acta pharm tox Kbh* 6 371
— (1951a) *Acta pharm tox Kbh* 7 119
— (1951b) *Ibid* 7 83
— (1951c) *Ibid* 7 103
— (1951d) *Ibid* 7 231
Thesleff S (1952a) *Acta physiol scand* 25 Fasc 4 368
— (1952b) *Ibid* Suppl 99
— (1955) *Proc 1st Congress of Internat Soc Anesth* Schreveningen
Thorsén G (1947) *Acta chir scand* Suppl 121
Waters R M (1946) *J Hist Med* 1 594
Wiklander O (1956) *Acta chir scand* Suppl 208

CHAPTER 22

TRENDS OF RESEARCH IN ANAESTHESIA IN THE UNITED STATES OF AMERICA

E M PAPPER

RESEARCH in anaesthesia in the United States of America has grown gradually but perceptibly in quality in the last two decades Many elements have contributed to this gratifying development Among the most important stimuli to the significant advances in anaesthetic research have been the contributions from the physical sciences the older disciplines in medicine and from the basic sciences Another significant factor has been the slow but increasing recruitment of physicians who wish to be trained in the research aspects of the specialty Finally, and quite interesting in understanding this process of growth is the increased support of research in the United States of America by government, industry and private *philanthropy*

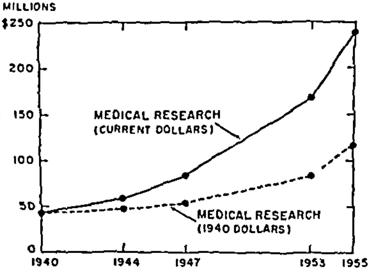
It will be necessary if one is to present even an approximately faithful picture of modern trends in research in anaesthesia in the United States of America to consider three major aspects which have influenced the patterns of development The first of these is the manner in which support is achieved for scientific research the second is the training and the recruitment of those who are to carry on research and the third aspect is the actual substance of research The order of listing these categories of interest is an arbitrary one for convenience of discussion When all is said and done the basic element upon which scientific research in anaesthesia or any other medical field depends is the skilful brain of the curious person Personnel are always the ultimate bedrock of importance in any such discussion

THE SOURCE OF RESEARCH FUNDS

So far as can be ascertained there is no complete information on the quantity or source of money which is spent solely for research in anaesthesia One can assume with reasonable certainty that the pattern of support of research for the medical sciences in general probably represents the manner of support for anaesthesia with one important exception It is more difficult in general to achieve substantial support on as wide a scale for research in anaesthesia than for a more traditional field This is a normal and natural consequence of dealing with a relatively new specialty that does not enjoy the dramatic appeal that can be marshalled for diseases such as poliomyelitis heart disease or cancer Be that as it may the extent of financial support for research in anaesthesia has gradually improved and continues to do so

In December, 1956 Shannon and Kidd discussed the trends of support for medical research thoroughly and completely They showed that the volume of support in dollars for medical research in the United States of America has increased from $40 000 000 to $240 000,000 between 1940 and 1955 This is rapid growth of support for research indeed but in 1955 it represented only 5 per cent of the support for all research and development in the United States of America a relative proportion that is small and essentially unchanged since 1940 If one also takes into account the change in the purchasing power of the dollar, the increased support in 1940 dollars is really only a threefold expansion as measured in terms of constant purchasing power rather than the sixfold increase that is apparent in terms of absolute values of dollars (Fig 29)

FIG 29—Expansion of medical research in the United States of America 1940-55 in terms of estimated current cost and 1940 purchasing power (*After Shannon and Kidd 1956 by courtesy of Science*)



Government sources

This change in total dollar support of medical research was also accompanied by a marked change in the origin of the sources of support In 1940 the contribution of the United States Government to medical research represented approximately 7 per cent of the total expended Because of military expediency in 1944, the Governmental contribution to medical research increased to 16 per cent of the total By 1955 the share of the United States Government in medical research had increased to more than 40 per cent or $113 000 000 of the $240 000 000 (Fig 30) It is most important to emphasize that the increases in Government support have not reduced the contributions from private philanthropy American industry or endowments Contributions to the support of research from all these sources have in fact increased although not in proportion to the degree of expansion of Governmental support

The largest single expenditure of funds for medical research occurs in the medical schools and the universities These institutions spend approximately 40 per cent of the total In academic institutions of the total expenditure for research only some 20 per cent is available from endowment income Approximately 30 per cent is made available by gifts from industry individuals foundations various types of health associations and other similar institutions The Federal Government provided approximately 50 per cent of the total amount of money spent by

the laboratories in the medical schools and the universities in 1955 If one recollects that only 20 per cent of the funds spent on research are from endowment it is painfully clear that the research money spent by the universities is controlled by outside institutions or agencies to the extent of 80 per cent of the total budget for medical research This past development suggests that increasing sources for funds for research will come from industrial resources, and to an even larger extent from the Federal Government

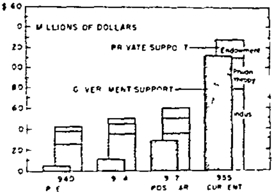


FIG 30—Cost of the medical research in the United States of America in four key periods showing sources of support (*After Shannon and Kidd 1956 by courtesy of Science*)

Industrial sources

Research in the medical sciences is of course also conducted outside the universities In pharmaceutical firms and other industries approximately $80 000 000 was spent in 1955 Much of this money was spent for developmental and specific pharmaceutical processes but substantial sums were also available for more basic studies The medical research laboratories which belong directly to the United States Government and its various Institutes and military installations had an operating budget of approximately $58 000 000 in 1955

Federal institutions

It must be obvious that a large degree of financial support is dependent upon the Federal Government It will be of some value to see how this actually operates The total Governmental expenditure for medical research is provided through several independent agencies The largest in terms of money is the Department of Health Education and Welfare Shannon and Kidd (1956) point out that support of medical research by independent agencies is not an inefficient way to support research Diversification assures minimal prejudice and preserves differences in points of view which are healthier for the scientific development of the nation In the final analysis the administrative decisions which are related to the support of medical research are matters of judgment and many different types of judgment can be brought to bear if separate and diverse agencies are involved rather than one monolithic control of the Governmental sources of financial support for research

There seems little doubt that there will be increasing amounts of Governmental money available for the support of medical research For the fiscal year of 1957 Governmental appropriations for the National Institutes of Health (only one of several Governmental agencies) rose to $183 000 000 This represents an increase

from $30 000 000 to $37 000 000 for the support of the Governmental laboratories of the National Institutes of Health in Bethesda, Maryland. Much more important is the fact that there is an increase of $78 000 000 over the previous year for research grants and for training purposes for non-Federal institutions. This increased appropriation is viewed as a significant opportunity to advance the development of medical and biological research as rapidly as possible.

TABLE I

Appropriations to the National Institutes of Health for the research grant programmes, fiscal year 1957, by categorical institute

(*After Shannon and Kidd 1956, by courtesy of Science*)

Institute	*Millions dollars*
Cancer	24.9
Heart	18.9
Mental health	11.4
Neurological diseases and blindness	9.6
Arthritis and metabolic diseases	8.1
Allergy and infectious diseases	8.1
Dental research	2.7
N.I.H. general	8.0
Total N.I.H. appropriation	91.7

Support related to disease categories

In the course of recent years the categorical approach to the support of medical science by disease—cancer, heart disease, neurological diseases and others—has apparently been difficult for some to understand. It should be recalled that any arbitrary system for the support of research, whether by specialty or by disease, is bound to present the same administrative problems and objections. The attitude of the advisory committees is broad, however, in that funds which carry a label of one disease category are appropriately available for fundamental research activities related to this disease. As an example, it is perfectly proper that the National Heart Institute support a basic study in hypothermia even though there may be no apparent or immediate direct application to the problems of heart disease. It is also proper that the Institute of Neurological Diseases and Blindness consider the support of fundamental physiological problems in the newborn period. This type of broad view of research makes possible a variety of investigator efforts, ranging from the most fundamental to the most applied. Anaesthesia fits these categories satisfactorily and support for projects in this field is available to some extent. (*See also* Table I.)

Method of allocating support

The method by which Federal funds are made available to investigators is of interest. The various granting agencies have as their scientific advisors groups of specialists formed into 'study sections'. These groups provide advice on the quality of the proposal for research and the ability of the persons who are requesting support. These judgments are reviewed by other groups, the National Advisory Councils, which include representatives of the lay public as well as scientists

These groups make their final recommendation to the granting agency This apparently complex but really quite simple system of advisory groups provides an assurance against uninformed and arbitrary judgment and is a method for preserving the freedom of research scientists as a group

Stability of support

Another important facet of the granting of support is the attempt to secure its stability There is a trend towards increasing the period of support for periods of 3 to 5 years This trend is balanced to preserve enough money for new investigators to enter the field Otherwise the obvious danger of excluding the development of new talent would be apparent There is also a trend towards increasing the size of single grants so as to minimize the amount of administrative and paper work Reducing the frequency of progress reports has also been of great assistance

THE TRAINING OF INVESTIGATORS

Because of the present situation in the United States of America it has become necessary to increase the emphasis on the training and recruitment of scientific manpower Federal funds are set aside to increase the opportunities for training The appropriation for research fellowships for example totals $33 500 000 for 1958 This is almost double the amount for the previous year The hope is that there will be an increasingly intensive training of physicians in the disciplines and methods of research similar to that which is available for the graduate training of other scientists

There has also been realization on the part of the Federal Government that this increasing number of trained scientists will require increased laboratory facilities Very few institutions now have adequate laboratory space Accordingly there has been legislation providing for a total of $90 000 000 over a 3-year period for assistance in the construction of medical research laboratories and other facilities To preserve private initiative the institutions which receive money under this Act are required to match it with their own funds

Thus the role of the Federal Government in the support of research has become of great importance The fact that this development has occurred without interference in the intellectual and scientific freedom of the research scientist is a tribute to the close and sympathetic understanding between research groups in private enterprise in the universities and medical schools in industry, and in the Federal Government This close collaboration will become even more important in the years to come

In examining the organization and support of research we have seen that the Federal Government is acutely aware of the need for developing and training qualified investigators in the medical sciences In the clinical field the relatively non traditional specialties require increased recruitment of people qualified to carry out research Examples are anaesthesia obstetrics and gynaecology physical medicine and rehabilitation

In anaesthesia the factors which oppose an increased flow of good people into research are fairly obvious There is the competition for qualified anaesthetists provided by the greater financial gain of private practice There is also the tendency

for many physicians intellectually qualified for fruitful careers in research, to enter one of the more traditional fields such as internal medicine or surgery These old and well established fields have better facilities for investigation and provide recognition for scientific accomplishment more readily, even though progress up the academic ladder may be slower It has become increasingly and even painfully obvious that the impetus to the training of competent people for research in anaesthesia must come from within the departments of anaesthesia particularly from those in the universities The reliance that could be placed on the pharmacologist or physiologist to be interested in anaesthetic problems and in that sense do our research for us has now disappeared So far as can be determined, consistent interest and study of the pharmacology of anaesthetic agents plays a prominent part in the programme of only two departments of pharmacology in the medical schools of the United States of America

The support for training will be available from the increased appropriation of Federal funds for fellowships from fellowships supported by private agencies or the medical pharmaceutical industries There is currently a feeling which is probably growing in strength that fellowships specifically devoted to anaesthesia should be made available in larger numbers as candidates of high quality in increasing numbers present themselves for such support

THE SUBSTANCE OF RESEARCH

The best anaesthesia research in recent years has been concerned with the acquisition of basic knowledge about the physiological derangements which occur in the anaesthetized state The development of newer anaesthetic agents and methods while important enough has been secondary to the understanding of the disturbances in normal function which are caused by anaesthetic agents

Ventilation

It will serve a useful purpose to outline to some extent a few of the problems that have been of interest to American anaesthesiologists in recent years Acid base balance and its relation to disturbed ventilation has been the source of much interesting study and a good deal of work in the last few years Interest in this field has been heightened by improved measuring devices better analytical techniques and the increased awareness that the popular practice of controlled respiration may incur the hazard of retention of carbon dioxide despite efforts to perform artificial ventilation efficiently Beecher and Murphy (1950) studied the problem in greater detail than had previously been undertaken during anaesthesia in man Subsequently other workers added further evidence that respiratory acidosis was a ready and rapid consequence of disturbances in ventilation during general anaesthesia (Gibbon and his colleagues 1950 Maier Rich and Eichen, 1951 Taylor and Roos 1950 Etsten 1953)

Appreciation of this situation raised several other interesting problems One was the effect of the rapid development of acidosis on the circulation Changes in electrical activity of the heart were demonstrated and haemodynamic effects after the correction of acidosis were also noted (Gertler Hoff and Humm 1946 Brown and Miller 1952) The most serious of these consequences was the relatively

high incidence of ventricular fibrillation and subsequent cardiac catastrophe if the retention of carbon dioxide were corrected too rapidly Evidence was also obtained that the retention of carbon dioxide may provide the background which makes cessation *of cardiac action possible during the stimulation of tissues which* are innervated by the vagus nerve (Sloan, 1950)

It became quite clear that one of the important keys to the acidosis situation during anaesthesia was the provision of efficient and adequate ventilation *continuously* This concept led to a renewed interest in the possibilities of mechanical ventilation The purpose of mechanical ventilators was in part convenience, but also the desire to provide effective oxygenation and removal of carbon dioxide without interruption, while permitting the anaesthetist reasonable freedom to carry on his other appropriate functions in the care of the anaesthetized patient Work with mechanical ventilators succeeded in the development of practical devices which are efficient for many purposes, and also stimulated at least two interesting lines of study The first of these was the development of respirators which may be used for research purposes One of these a device designed by Frumin and Lee (Frumin, 1957) is in effect a mechanical analogue of the respiratory centre in that ventilation is automatically governed by the concentration of carbon dioxide at the end of exhalation through a servo system which activates the mechanical part of a respirator This device has been fruitfully employed for clinical anaesthesia when used with nitrous oxide, oxygen and suxamethonium It has also been used for important physiological studies during anaesthesia because it permits precise control of several important parameters of anaesthesia and ventilation Another direction of research in the mechanical ventilator field has been the effort to study each of the variables of respiration independently Holaday and Gilroy (1957) have constructed a machine which will be useful for the study of each aspect of ventilation independent of other aspects of the breathing process

An interesting and obvious consequence of these lines of work has been observation of the fact that satisfactory ventilatory patterns may have harmful influences upon the circulation The direction of interest in the future will be to define more precisely the effects on the circulation of newer types of mechanical ventilators and to determine where possible the influences of these devices upon the blood flow in specific organs

Muscle relaxants

A field of great interest in the United States of America has been study of the muscle relaxants These agents enjoy much popularity in clinical use and fortunately have excited considerable interest in their basic pharmacological actions *d* Tubocurarine has been studied extensively in recent years by Marsh (1952) who found that the drug was distributed universally in the body and that there was no increased concentration at the myoneural junction In man the plasma concentration initially reached a theoretical maximum almost at once and began to diminish very rapidly In less than 10 minutes the plasma level fell to approximately two thirds of the original Marsh also demonstrated that 30 per cent of the administered dose was excreted in the urine He concluded that the duration of the paralytic action of *d* tubocurarine after one injection was related to the rapid redistribution and not to the rate of metabolism or the rate of

excretion of the drug With repeated doses after all depots were saturated the paralytic action became prolonged and was then more dependent upon the rate of metabolism and excretion There has been considerable interest in the question of the central action of this drug and the other relaxants At the present time studies have not defined in clear-cut fashion whether there is a central action or not In general the evidence seems to be that the action of the relaxants is primarily peripheral

The particular choice of relaxant seems in part at least to be determined by previous teaching and perhaps in some degree by habit At a guess it is a reasonable assumption that suxamethonium is the most popular relaxant in the United States of America at the present time The question of prolonged apnoea after suxamethonium has been of some interest in recent years However it has been shown independently by several workers that the nature of the block produced by this drug appears to change after either prolonged administration or relatively large doses The block under these conditions comes to resemble more closely that produced by *d* tubocurarine It is relieved by edrophonium (Tensilon) in dosage comparable to that used for relief of block with *d* tubocurarine (Foldes 1957, Schweiss and Frumin 1957)

Reticular system of the brain-stem

There has also been increasing interest in the basic mechanism of the anaesthetic state as a result of the recent studies of French Verzeano and Magoun (1953) and Arduini and Arduini (1954) on the physiology of the reticular system of the brain stem These workers observed in the cat and monkey that excitation of the central part of the cephalic brain stem caused arousal of dormant animals and destruction of this area produced a state of chronic coma They concluded that the reticular activating system appeared to exert a desynchronizing influence on cortical and diencephalic structures in the state of wakefulness Anaesthesia produced selective depression of this area whereas activity in the lateral direct sensory pathways and sensory cortex were unaltered These findings suggest that depression of activity in this area and the cortical interneuronal system participate to a major degree in the production of the anaesthetic state

Electroencephalography studies

Other studies carried on by Faulconer Bickford and their associates (Faulconer 1952) on the electroencephalograph during anaesthesia are consistent with the hypothesis of Magoun Studies with the aid of the electroencephalograph have been productive in the United States of America One of the lines of study has been the effort to define depths of anaesthesia more precisely with some clear reference to an objective measurement that is easier to accomplish than the measurement of gases in exhaled air or in the blood stream A second interest in this method of measurement has been to use it for the study of cerebral function during anaesthesia

Local, regional and spinal anaesthesia

There has been undiminished clinical interest in the field of local regional and spinal anaesthesia but a lack of activity in carrying on precise and quantitative studies There has been some advance in knowledge in the mechanism of epidural

block and there has been considerable interest in the matter of neurological damage after spinal anaesthesia The studies of Dripps and his associates (Dripps and Vandam 1954) clearly demonstrate that the neurological complications of this method have been greatly over emphasized

Studies of the newborn

There has been interest in the newborn period and in providing safe and efficient anaesthesia for the obstetrical patient The studies in the newborn have involved both clinical methods and precise laboratory techniques A scoring system designed by Apgar (1953) has gained widespread acceptance in the United States of America to evaluate the condition of the newborn A total score of 10 indicates that the infant is in the best possible condition and a score of 0 signifies a dead infant The factors which are measured are the heart rate, respiratory effort muscle tone response to catheter stimulation in the nostril and skin colour Apgar is in the process of planning a follow up study on the outcome of some 10 000 newborn infants who have been scored by her system In the field of precise measurement, Apgar and her associates (1955) reported on over 200 infants whose capillary blood oxygen was measured shortly after birth At the age of 5 years the children studied were subjected to certain intelligence tests There did not appear to be any correlation between capillary blood anoxia at birth and subsequent intelligence at the age of 5 years Obviously factors other than neo natal oxygenation influence the subsequent development of mental function However this study does suggest that non fatal anoxia may not result in cerebral damage that can be demonstrated with standard intelligence tests At the present time studies in the physiological readjustments of the circulation immediately after birth have been undertaken The results of these studies should be of considerable interest

Barbiturates

There has also been continued interest in the United States of America in the development of anaesthetic barbiturates (Brodie and his colleagues 1950) Since the quantitative studies of thiopentone were reported other anaesthetic agents in this class have been developed and subjected to similar scrutiny Up to the present time the anaesthetic barbiturates have shown relatively little difference one from the other despite the considerable clinical interest in the newer compounds particularly thiamylal (5 allyl 5 (1 methylbutyl) 2 thiobarbituric acid sodium salt) and methothiourate (Neraval Thiogenal sodium salt of 5 (2 methylthioethyl) 5 (1 methylbutyl) 2 thiobarbituric acid) The pattern of rapid organ penetration extensive fat localization and side chain oxidation described for thiopentone seems to be the basic pattern which the body uses for the deposition of all the anaesthetic barbiturates

The study of subjective phenomena

A most interesting development in anaesthetic research in the United States of America has been the effort to study subjective phenomena by objective means Beecher and his associates have been leaders in this particular field (Denton and Beecher 1949) The problems of pain discomfort anxiety and the related

subjective responses to factors which stem from the operative and anaesthetic experience have been most difficult to evaluate Analgesics anti emetics and sedatives have been introduced over the years in great profusion with poor evidence to support the particular virtues of the various drugs The emphasis on the importance of controlled studies and the use of the double blind technique in anaesthesia has been an important contribution of the Harvard group These studies defined, with greater precision, the nature of post operative pain the value of old and new analgesic drugs and have pointed the way toward experimental situations which can be used for the study of drugs and analgesic methods in the future

Cardiovascular surgery

Anaesthetic research has also been concerned with assisting surgical developments in operations upon the heart Studies in hypothermia have been advanced greatly by the work of Swan and his colleagues (1953) Extracorporeal circulation has been made practical by Kirklin and his colleagues (1955) and Worden and his colleagues (1954) and the anaesthetist has been a helpful co worker with his surgical colleague in these attempts to develop practical and successful approaches for the correction of cardiovascular abnormalities

Simplification of instruments

Another significant trend of research in the United States of America has been the effort to simplify precision instruments to assist the clinician in the more effective care of his patient There has been a salutary and reasonably rapid advance in the breadth of thinking in this field which has produced a change from unfortunate resistance to quantitative instruments in the operating room to eager acceptance The clinician in anaesthesia now realizes more than ever before that the more information he has at his command the better he is able to take effective care of his patients This attitude has encouraged the development of a variety of precision instruments which can be made sturdy enough for operating room use reasonably simple to operate for the physician—who is after all not an aeronautical engineer—and safe from the standpoint of fire and explosion Not many of these instruments are generally available as yet but it is not unusual in a modern operating room to find an electrocardiograph, an electro encephalograph a ventilation meter and a method for measuring the pressures developed during normal or controlled respiration It has become increasingly apparent that the provision of instruments which will measure efficiently the concentrations of the common gases such as carbon dioxide and oxygen monitor and record the blood pressure the heart rate the respiratory rate and volume are the next goals for the practical translation of research into clinical care

REFERENCES

Apgar Virginia (1953) Proposal for New Method of Evaluation of Newborn Infant *Curr Res Anesth* 32 260

— Taylor H C McIntosh R and Girdany B R (1955) Neonatal Anoxia I A Study of the Relation of Oxygenation at Birth to Intellectual Development *Pediatrics* 15 653

Arduini A and Arduini M G (1954) Effect of Drugs and Metabolic Alterations on Brain Stem Arousal Mechanism *J Pharmacol* 110 76

Beecher H K and Murphy A J (1950) Acidosis During Thoracic Surgery *J thorac Surg* 19 50
Brown E B Jr and Miller F (1952) Ventricular Fibrillation following Rapid Fall in Alveolar Carbon Dioxide Concentration *Amer J Physiol* 169 56
Brodie B B Mark L C Papper E M Lief P A Bernstein E and Rovenstine E A (1950) The Fate of Thiopental in Man and a Method for its Estimation in Biological Material *J Pharmacol* 98 85
Denton J E and Beecher H K (1949) New Analgesics I Methods in Clinical Evolution of New Analgesics *J Amer med Ass* 141 1051
Dripps R D and Vandam L D (1954) Long Term follow up of Patients who received 10 098 Spinal Anesthetics *J Amer med Ass* 156 1486
Etsten B E (1953) Respiratory Acidosis during Intrathoracic Surgery (Overholt) Prone Position *J thorac Surg* 25 286
Faulconer A Jr (1952) Correlation of Concentrations of Ether in Arterial Blood with Electro-encephalographic Patterns occurring during Ether–Oxygen and during Nitrous Oxide Oxygen and Ether Anesthesia of Human Surgical Patients *Anesthesiology* 13 361
Foldes F F (1957) Personal communication
French J D Verzeano M and Magoun H W (1953) Neural Basis of Anesthetic State *Arch Neurol Psychiat Chicago* 69 519
Frumin M J (1957) The Clinical Use of a Physiologically Oriented Respirator delivering N_2O-O Anesthesia *Anesthesiology* In Press
Gertler M M Hoff H E and Humm D G (1946) Acid Tolerance of Dog Heart *Amer J Physiol* 146 478
Gibbon J H Allbritten F F Jr Stayman J W and Judd J M (1950) Clinical Study of Respiratory Exchange during Prolonged Operations with Open Thorax *Ann Surg* 132 611
Holaday D A and Gilroy J (1957) Personal communication
Kirklin J W DuShane J W Patrick R T Donald D E Hetzel P S Harshbarger H G and Wood E H (1955) Intracardiac Surgery with the Aid of a Mechanical Pump-Oxygenator System (Gibbon Type) Report of Eight Cases *Collected Papers of the Mayo Clinic and the Mayo Foundation* XLVII
Maier H C Rich G W and Eichen S (1951) Clinical Significance of Respiratory Acidosis during Operations *Ann Surg* 134 653
Marsh D F (1952) Distribution Metabolism and Excretion of *d* Tubocurarine Chloride and Related Compounds in Man and Other Animals *J Pharmacol* 105 299
Schweiss J F and Frumin M J (1957) Personal communication
Shannon J A and Kidd C V (1956) Medical Research in Perspective *Science* 124 1185
Sloan H E (1950) Vagus Nerve in Cardiac Arrest Effect of Hypercapnia, Hypoxia and Asphyxia on Reflex Inhibition of Heart *Surg Gynec Obstet* 91 257
Swan H Zeavin I Blount S G Jr and Virtue R W (1953) Surgery by Direct Vision in the Open Heart during Hypothermia *J Amer med Ass* 153 1081
Taylor F H and Roos A (1950) Disturbances in Acid Base Balance during Ether Anesthesia with Special Reference to Changes Occurring during Thoracic Surgery *J thorac Surg* 20 289
Worden H E Cohen M DeWall R A Schultz E A Buckley J J Read R C and Lillehei C W (1954) Experimental Closure of Interventricular Septal Defects and Further Physiologic Studies on Controlled Cross Circulation *Surg Forum* 22

INDEX

Beecher H K and Murphy A J (1950) Acidosis During Thoracic Surgery *J thorac Surg* 19 50

Brown E B Jr and Miller F (1952) Ventricular Fibrillation following Rapid Fall in Alveolar Carbon Dioxide Concentration *Amer J Physiol* 169 56

Brodie B B Mark L C Papper E M Lief P A Bernstein E and Rovenstine E A (1950) The Fate of Thiopental in Man and a Method for its Estimation in Biological Material *J Pharmacol* 98 85

Denton J E and Beecher H K (1949) New Analgesics I Methods in Clinical Evolution of New Analgesics *J Amer med Ass* 141 1051

Dripps R D and Vandam L D (1954) Long Term follow up of Patients who received 10 098 Spinal Anesthetics *J Amer med Ass* 156 1486

Etsten B E (1953) Respiratory Acidosis during Intrathoracic Surgery (Overholt) Prone Position *J thorac Surg* 25 286

Faulconer A Jr (1952) Correlation of Concentrations of Ether in Arterial Blood with Electro-encephalographic Patterns occurring during Ether–Oxygen and during Nitrous Oxide, Oxygen and Ether Anesthesia of Human Surgical Patients *Anesthesiology* 13 361

Foldes F F (1957) Personal communication

French J D Verzeano M and Magoun H W (1953) Neural Basis of Anesthetic State *Arch Neurol Psychiat Chicago* 69 519

Frumin M J (1957) The Clinical Use of a Physiologically Oriented Respirator delivering N_2O–O_2 Anesthesia *Anesthesiology* In Press

Gertler M M Hoff H E and Humm D G (1946) Acid Tolerance of Dog Heart *Amer J Physiol* 146 478

Gibbon J H Allbritten F F Jr Stayman J W and Judd J M (1950) Clinical Study of Respiratory Exchange during Prolonged Operations with Open Thorax *Ann Surg* 132 611

Holaday D A and Gilroy J (1957) Personal communication

Kirklin J W DuShane J W Patrick R T Donald D E Hetzel P S Harshbarger H G and Wood E H (1955) Intracardiac Surgery with the Aid of a Mechanical Pump-Oxygenator System (Gibbon Type) Report of Eight Cases *Collected Papers of the Mayo Clinic and the Mayo Foundation* XLVII

Maier H C Rich G W and Eichen S (1951) Clinical Significance of Respiratory Acidosis during Operations *Ann Surg* 134 653

Marsh D F (1952) Distribution Metabolism and Excretion of *d* Tubocurarine Chloride and Related Compounds in Man and Other Animals *J Pharmacol* 105 299

Schweiss J F and Frumin M J (1957) Personal communication

Shannon J A and Kidd C V (1956) Medical Research in Perspective *Science* 124 1185

Sloan H E (1950) Vagus Nerve in Cardiac Arrest Effect of Hypercapnia, Hypoxia and Asphyxia on Reflex Inhibition of Heart *Surg Gynec Obstet* 91 257

Swan H Zeavin I Blount S G Jr and Virtue R W (1953) Surgery by Direct Vision in the Open Heart during Hypothermia *J Amer med Ass* 153 1081

Taylor F H and Roos A (1950) Disturbances in Acid Base Balance during Ether Anesthesia with Special Reference to Changes Occurring during Thoracic Surgery *J thorac Surg* 20 289

Worden H E Cohen M DeWall R A Schultz E A Buckley J J Read R C and Lillehei C W (1954) Experimental Closure of Interventricular Septal Defects and Further Physiologic Studies on Controlled Cross Circulation *Surg Forum* 22

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